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NASAL FUNCTION AND NASAL NEUROSIS

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THE nose is primarily an olfactory organ, since this is the only one of its functions which cannot be taken over by another body tissue. Anosmia, although occasionally a blessing, is a common complaint of a great many of our patients. Excepting for lesions affecting the cribriform plate itself, anosmia is secondary to the other conditions about to be discussed.

The secondary functions of the nose are many. The nose is an organ of curiosity when we poke our noses into something, or of exploration when we nose out a fact. It is an organ of persuasion, actively, as when we lead someone by the nose, and passively when we are led by the nose or poked in the nose. It is a measure of intelligence when we do not see beyond our noses, and of vision when something not seen is right under our noses. Emotionally, it expresses jealousy when our noses are out of joint, and comedy when it belongs to, say, Mr. Durante. The nose is also, we must not forget, one of the secondary sexual organs.

In the male dog, in whom the more important qualities of man can be observed and studied in their more obvious and perhaps primitive aspects, oblation of the cribriform plate is as efficacious as castration. A canine male with anosmia becomes quite philosophical about his sex life. In humans, especially among the aborigines, rubbing noses is a sign of affection, while with more advanced races the use of perfume is considered to be a sign of the highest degree of civilization. Since in man the sense of smell is relatively undeveloped, the female of the species improves upon nature, as she does in other ways, with products of the perfumer's art quite blatantly labeled for the purpose for which they were created, namely,

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My Sin, Surrender and Tabu. This last applies, at least, for the moment. Interestingly enough, the French perfumes are reportedly the most potent in this regard, perhaps because the French are supposedly the greatest experts in matters pertaining to sex. As a matter of fact, they are not more expert than anyone else—they just talk about it oftener and for longer periods of time.

To discuss more mundane matters, the nose is, as we all well know, related to the endocrine system. It participates in any of the changes affecting the mucous membranes associated with gonadal relationships and responds to endocrine preparations applied locally, taken orally, or injected subcutaneously. Alcohol, which causes congestion of such sexually associated mucous membranes, also does the same for the nose. The English texts discuss post-festival (excessive alcoholic ingestion) colds, and the German texts describe the syndrome of the running nose of the sexually stimulated but otherwise unrequited young woman. When, among the French and German peasants, such coryza ceases without treatment, and before marriage, there is a saying to the effect that the girl is no longer watering after cake crumbs because she is really eating cake.

When such patients appear at our offices it is always wise to discuss with them this subject. If they plan to marry in the near future, it is well to send them off with reassurance, a blessing, mild symptomatic medication, and instructions to return, if necessary, after the honeymoon. They get well just often enough to make certain types of statistical studies questionable in value.

It is not surprising that an organ which participates in smell and, to a much lesser degree, in sex, should be involved with the psyche. All three may be mutually and coincidentally interrelated, but we sometimes see psychic forces alone causing nasal changes, as in anger and in fear. There are a number of patients under observation at present whose unhappiness with their husbands is directly related to their nasal blockage, the condition clearing as the relationship improves and recurring as it deteriorates. In one patient, any antihistamine will clear her cold on pay day, in three doses, especially if her husband returns home sober and with an intact pay check. At other times, antihistaminic agents have no effect whatsoever, which is not at all surprising.

Psychic changes in the nose are apparent in the so-called "diplomatic cold," which appears when necessary to its owner and vanishes just as readily when it is no longer needed. "Monday morning colds" fit into this category, as do those seen on the first day of school and on the first day of examinations. Psychiatrists are accustomed to such colds as signs of resistance when they serve as excuses to break appointments. The analyst tends to become especially annoyed with these excuses, since they see more of this type of nasal symptomatology than we do. There is the story of the Boston analyst who was called to the telephone by the patient's maid with a story that this time it was not a cold, but a broken nose, a seriously

broken nose. "It has been," said the maid, "broken in three places." "Very well," said the doctor, siphoning off his own hostility. "Tell her I'm sorry, but I hope it will teach her to keep her nose out of those places."

The functions mentioned have been occasionally and really secondarily annoying to most patients. The nose has a prime function it normally exercises continuously. It is a complex air-conditioning apparatus which must filter, warm and moisten the air which passes through it twenty-odd times a minute, twenty-four hours a day. Malfunction of this apparatus is the cause of much nasal symptomatology. Warming air and moistening it go together since the mucous membrane can hardly do one without doing the other, especially since air is not always ideally cool and dry. If we wish to follow the cycle of events, we must begin with a patient properly dressed and in a room at 72 degrees with 40 per cent humidity. If the patient goes outdoors not properly dressed, cold air touching the skin and mucous membrane sets into motion the nasal cutaneous reflex arcs, which result in contraction of the cutaneous vessels and dilatation of the nasal vessels. The cold, dry air must be warmed and moistened. If the change is too great or too sudden, the excess moisture will develop into the typical coryza. If, for any reason, the nasal passages are narrow, there may be blockage as well. These patients often think they are coming down with a cold. Properly clothed, normal individuals are not conscious of these nasal changes. In oversensitive patients, the coryza may last for as long as the patient is exposed to the physical agent, namely, the cold air. Cold water on the skin acts similarly.

A patient may be outdoors with his nose attuned to cold, dry air and return indoors. The skin is warm and the nasal membranes become less turgid. The warm air needs little warming. It may, however, if dry, need much moistening. Again, the patient may respond with excess moisture and transient coryza. It often occurs that the air is both warm and moist, as in a restaurant. Here, normal individuals coming in from ice skating or skiing will develop a coryza while the nasal membranes adjust from excreting maximum moisture to normal minimal needs. A bowl of hot soup or hot coffee will augment the amount of coryza to an embarrassing quantity, lasting in normal individuals several minutes. In those in whom the adjustment is faulty, absent, or sluggish, the nose may run for hours. Taking a hot bath will also bother such patients, to whom we often apply the diagnosis of physical allergy, in this case, to heat.

What of malfunction of filtration? This is naturally enough allied to the sense of smell. Noxious particles cause the sneeze reflex, and noxious or irritating fumes, the Brodie-Dixon reflex. Just as relaxation of any sphincter of the gastrointestinal tract causes all those distal to it to relax so in its way stimulation of certain areas of the nasal mucosa causes all sphincter-like distal tissues to contract or go into spasm. The use of smelling salts is, of course, based on the recognition of this phenomenon. And so, also, is our so-called nasogenic asthma. The fumes of fresh paint,

highly heated frying oil, refrigerants, ammonia and oil stoves may all in part act this way. Cold air itself may serve as an irritant of this type and cause asthma. Cocainising the nose will neutralize the effect of the irritant fumes or cold air and prevent the spasm.

Independently of the physical factors or the neuroses, the nose is intimately related to stress syndromes, especially physical stress. In concentration camps, the so-called "hunger edema" is associated with nasal coryza as an early sign of water retention of the nutritional type. It ceases when sufficient food intake corrects this hunger edema. Such physical stress and nasal symptomatology is relieved by ACTH, as you know. This same drug, of course, is responsible for emotional changes, relieving nasal symptoms, therefore, by two mechanisms, or perhaps when we know them better we may discover them to be a single mechanism.

A typical nasal neurosis is due to none of these factors, although it may be initiated by any experience which draws the patient's attention to his nose. It may thereafter continue in its own right. The patient presenting the syndrome insists that he has nasal blockage despite all objective evidence that the nasal passages are sufficiently patent. He will sniff with great force and insist that the resulting noise is due to a blocked nose. With each successive forcible sniff, of course, the blockage, originally not present, develops and increases. Sniffing hard does cause a noise since the air must pass with greater velocity through a smaller opening. Persistence of sniffing causes a reflex congestion of the membranes which react as though they must warm, filter, and moisten this faster-than-usually-moving air. Anyone who wishes to try it will quickly discover how queer his nose feels for sometime afterward. This type of nasal neurosis is the equivalent of other organ neuroses such as the pseudo-angina syndrome.

Having once become mildly conscious of his nose, the patient becomes increasingly so. It is as though the central threshold of sensitivity has become definitely lowered for the reception of peripheral nasal stimuli. Whether or not this is a reciprocal reflex and the effect of the heightened nasal consciousness does not itself interfere with the nasal function is a moot point, but this, in lesser degree, probably also takes place.

In order to discover whether or not his nose is clear, the patient continues to sniff forcibly through his nostrils. He does not know that the forcible nasal inspiration acts reflexly to close the nostrils and to make inspiration audible. Any mucus present in normal amount is forcibly driven toward the nasophraynx. Hawking brings it to a position in which it may be expectorated or swallowed. The patient now has an increased consciousness regarding this nasopharyngeal mucus, and here again finds himself wondering whether such mucus is present and therefore continuously attempts to bring the normal secretion within reach. At this stage in the development of his neurosis, he complains of a post-nasal drip.

Demanding, increasingly, a meticulous clarity of the nasal passages, he submits to medicine or surgery. Usually a turbinectomy has been performed. The greater air space may satisfy the patient and bring his neurosis to an end, or he may grow accustomed to his condition and demand more of an airway. This may be achieved by electrocoagulation, and following further surgery, nasal reactions to environmental stimuli as heat and cold, aridity and humidity cause either abnormal reaction or normal reactions abnormally interpreted.

At this point, the patient begins to depend upon nose drops. His standard of normality quickly changes. He accepts the cool-feeling, constricted membrane as representing a normality instead of an abnormality. The fact that he gets a similar satisfaction from menthol, which feels cool, although it does not shrink the membranes, proves that the difficulty lies in the patient's sense of perception and not in the amount of air space available. The original Benzedrine inhalor developed an entire generation of nasal neurotics, many of whom were the physicians who were given inhalors without charge. The clear nose and the mild euphoria were equally as habit forming. The open, clear nose, the sense of coolness in the passing air, and the feeling of alertness, were irresistible to many patients. In some it became an obsession. Antihistaminic agents can be used in treatment, but frequently with no results, excepting as they are sedative in effect. Nose drops will work in such patients, especially the strong vasoconstrictors like Privine.

The only desirable treatment lies in re-educating the patient. Explanation and insistence upon the use of progressively milder and milder constrictors will often help. The usual treatment period is from several weeks to several months after all other causes of nasal pathological reactions have been removed.

In some cases the neurosis is not locally in the nose, but rather the nose is the organ chosen for a general neurotic constellation. These are the patients to whom, in bawdy language, "everything stinks." They truly need psychiatric treatment, for which our injection therapy is only a partial and a poor substitute.

It is quite obvious that the nose is a fascinating organ. Its aberrations are many and varied. Treatment directed against the chief complaint must also take into consideration functional symptoms.

75 Bay State Road

REQUESTS FOR ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY

A Fellow of the College is desirous of obtaining back copies, 1937 to date, of the *Archives of Dermatology and Syphilology*. Any reader who has, or knows of anyone who has, for sale any issues of this periodical may write to Brian H. R. Hill, M.D., F.A.C.A., Bowman's Building, Market Street, Napier, New Zealand. Information may also be sent to F. W. Wittich, M.D., Secretary-Treasurer, American College of Allergists, 401 LaSalle Medical Building, Minneapolis 2, Minnesota.

THE ROLE OF FOOD SENSITIVITY IN NASAL ALLERGY

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CONTROVERSY concerning the importance of sensitivity to foods in the production of allergic reactions continues without ceasing. Various authors, referring to food sensitivity as a cause for the production of nasal allergy, use many contradictory terms, such as "common," "uncommon," "often," "frequent," "food causes," "frequent, but less important than pollens," "in seasonal hay fever rarely," "occasionally caused by seasonal fruits and seasonal vegetables," "pollen patients often sensitive to foods," "occurs most often in children under ten." In the discussion of seasonal hay fever, some authors do not even mention the fact that food sensitivity may play any part.

Characteristic of those who do not believe in food allergy as a cause of nasal symptoms is the statement "contrary to usual belief, it is uncommon." Characteristic of those who do believe in its frequent occurrence is the statement "much more common than usually believed."

Some authors mention the fact that "post-nasal catarrh," "chronic sinus," and "chronic or recurring colds" are often due to food sensitivity. In percentage it has been estimated that food allergy is a cause of nasal symptoms in 2 per cent, 3 per cent, 5 per cent, 9 per cent, 10 per cent, something over 20 per cent, 33 per cent, and in over 50 per cent of the cases of nasal allergy. We may conclude that whatever the truth is, it has not yet been proved.

Characteristics of nasal symptoms produced by food sensitivity vary somewhat, as does the percentage. One author states that the symptoms are worse in cold weather, worse when the patient is away from the ocean, and that there is more marked nasal blockage, loss of smell, and polyp formation than when the symptoms are due to inhalants. Sneezing attacks are severe and paroxysmal. There is less itching comparatively than in pollen and inhalant cases.

Others state that if despite properly administered treatment for sensitivity to inhalants there is still marked itching of the nose, of the soft palate, of the upper lids of the eyes, and of the inner canthus, we must suspect food allergy.

Attacks, or exacerbations, tend to appear at night or in the early morning. Other exacerbations may begin suddenly and last from two hours to three days. Characteristic also is the profuse production of mucus and marked obstruction.

Ideas vary a great deal concerning the relative importance of foods as

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to frequency in producing nasal allergy. Some foods rated important by one physician are not mentioned by others. The following list of foods shows those given in order of relative importance from three sources.

Wheat	1	2	1
Milk	2	3	3
Eggs	3	1	2
Fish	4	6	7
Chocolate	5	9	4
Cabbage group	6	0	0
Orange	7	0	0
Apple	8	0	0
Banana	9	0	0
Melons	10	0	0
Berries	11	10	0
Nuts	12	5	5
Spices	13	0	0
Tea	14	0	0
Coffee	10	0	0
Peas and beans	0	4	6
Onions	0	7	0
White potato	0	8	0
Cantaloupe	0	11	0
Fruit	0	0	8

Another writer mentions only fruits and vegetables:

Beans and peas	Berries
White potato	Melons
Onions	Citrus
Tomatoes	Banana
Garlic	Apple
Celery	Grape
	Pears
	Pineapple
	Cherries

One author rates in turn vegetables, cereals, fruits and condiments, as causing nasal allergy, and says that milk and eggs seldom produce these symptoms.

The following report is the result of study of 368 patients in whom a diagnosis of allergic coryza was made. They have been selected at random from our cases having been examined and treated during the last five years. Their ages range from a few months to over eighty years. Males and females are represented approximately equally.

The diagnosis of food sensitivity has been based on the production of definite symptoms two or more times by the ingestion of a food when no other cause could be demonstrated. Any method of diagnosis based on patients' opinions and observations will carry with it some inaccuracy. However, we have no other practical way at the present time of reaching conclusions concerning this matter. Often even when we have the patients in the hospital or in our office for observation and food testing, psychosomatic factors and other causes may invalidate the observations.

Food sensitivity was rated as the primary or major cause of nasal symptoms when it was the only cause for the symptoms, or when food sensi-

tivity was greater than inhalant sensitivity or equal to it. Food sensitivity was rated as secondary or a minor cause of nasal symptoms when it was of less importance than inhalant sensitivity but when symptoms could be produced on the ingestion of foods under the proper circumstances. In some instances, food sensitivity caused nasal symptoms under very unusual circumstances: only, that is, when the patient was emotionally upset, or when ingestion of food occurred along with other causes, or when the patient was already having symptoms, or when there were marked weather or atmospheric changes.

In thirty patients the only complaint was hay fever. Of these, food was a factor in seven and had no effect on twenty-three. In eighty patients, the chief complaint was hay fever, but there were other allergic manifestations. Food was a factor in the production of symptoms in twenty-eight and not a factor in fifty-two. In 221 patients there was a chief complaint of asthma, with definite symptoms of nasal allergy. Food produced nasal symptoms in ninety-four of these patients and no ascertainable symptoms in 127.

In twenty-seven instances symptoms of asthma and of hay fever were about equal in their severity. In these patients foods caused nasal symptoms in eleven and none in sixteen. In ten patients some other form of allergy besides asthma and hay fever was the chief complaint, along with nasal symptoms as a minor complaint. Two of these had symptoms produced by foods and eight didn't. One hundred and forty-two patients (38 per cent) gave clinical reactions to the ingestion of foods. In eleven of these 142 patients food was a major cause of nasal allergy, in 110 a minor cause, and in twenty-one a cause under unusual circumstances only.

In those patients who had nasal symptoms in some particular season only, 16 per cent had symptoms produced by food ingestion. In patients with severe seasonal symptoms, but minor perennial symptoms, food sensitivity was present in 36 per cent; in patients with perennial symptoms only, 25 per cent; and in patients with perennial symptoms with seasonal exacerbations, 44 per cent. In these patients the reaction time for the production of symptoms varied from a few minutes to twenty-four hours. The amount of food required to produce symptoms varied from a very small amount in some to the necessity for accumulation of foods from two to five days in others.

In the 142 patients, the relative frequency of occurrence of the more important foods is shown below.

1. Chocolate
2. Milk, wheat
3. Citrus fruits
4. Eggs—banana—cabbage family
5. Tomatoes
6. Corn—apples
7. Pork—onions
8. Peas and beans
9. Coffee—cola—tea

Sudden and violent nasal reactions were obtained in some patients to the ingestion of chocolate, corn, and bananas. In our series these three foods produced the quickest and the severest reactions described by patients.

Chocolate by far outranked all the rest. Milk and wheat were equal. Eggs, bananas, and the cabbage family were equal, as were corn and apple, and pork and onions. Coffee, the cola drinks, and tea were considered as a group and ranked ninth.

In the 368 patients there occurred thirty other manifestations of allergy than allergic coryza and asthma. Symptoms of gastrointestinal allergy were present in 100 patients, urticaria and/or angioedema in seventy-one, some form of dermatitis in sixty-five, cerebral symptoms in eighteen, and headaches in seventeen.

Much to my surprise, food sensitivity in these cases appeared to be important at all ages. I had formerly held the idea that in children from the ages from one to ten we could prove the existence of food allergy much more easily and in a larger percentage of patients than in those who were older. We had some youngsters who had no history of food sensitivity and in whom we could never prove its presence. We had some very old people in whom it was fairly easy to prove that foods could cause nasal symptoms. We must remember, therefore, that food sensitivity may be important at any age.

Certain other facts were illustrated in these patients. The longest time that we could prove it was necessary for a food to act cumulatively and produce symptoms was five days. In some patients we had definite evidence of the summation effect of taking more than one food at one time to produce allergic symptoms, or of a food taken along with exposure to inhalants giving a much worse reaction.

In some patients the symptoms of food sensitivity were much worse in cold weather. It was not unusual for a patient not to be able to take a food in a concentrated form, but to be able to eat it when mixed with other foods. Some patients could not take a food early in the morning, but could take it later in the day after eating other foods. Some patients could take a food during the day, but could not take it at night. Some foods would produce an increase of symptoms in patients in whom attacks had already started, but would not cause any effect at other times.

It is not infrequent that odors of foods or of foods cooking will cause symptoms. It was known to some patients that they could eat veal, but not beef, and certainly some patients seemed to be able to tolerate rooster meat when they could not take that of hens. Some patients markedly improved while on the diet, but when they broke diet the symptoms gradually developed again. When returning to their diets they were relieved of these symptoms. Specific sensitivity to any one food was

never proven. These cases were, of course, not listed as true food sensitivity.

It was evident that foods often caused specific symptoms. One might cause sneezing and a discharge, another might cause obstruction only, and another might cause itching without any other symptoms. At times a food would cause nasal allergy but no other symptoms. In the same patient another food would cause other allergic manifestations but no nasal symptoms.

Having examined these patients, watched them through treatment, and checked their charts in detail, I find it difficult not to believe that food sensitivity does have a definite part in the production of nasal symptoms. It is probable that food sensitivity seldom plays the major role in the production of seasonal hay fever, but it does play a role in a sufficient number of cases to demand consideration. In many of our patients with a chief complaint of asthma but with lesser nasal symptoms, the asthma has been easily controlled (either partially or totally relieved), but nasal symptoms persist. It is likely that in some of these patients food sensitivity is responsible for the continuation of nasal symptoms.

I have no doubt that had I selected 368 other cases of nasal allergy the percentage of occurrence of food sensitivity would not be the same as in these. As time goes on, I would expect it to be higher, because the longer I practice allergy, the better I think I understand food sensitivity, and know how to look for it. It is quite possible that in no instance have we exhausted the possibilities of diagnosis.

CONCLUSIONS

Food sensitivity causes nasal allergy. In some cases it assumes a primary or major role, in others a secondary or minor role, and in still others is active only under unusual circumstances. In any patient with nasal allergy who has been considered as adequately treated from the standpoint of inhalant sensitivity, but in whom symptoms persist, food sensitivity must be considered. In patients with seasonal allergic coryza, presumably due to pollens, and who have no history of food allergy, it is wise to test with pollens and treat with pollen extract only, or if necessary, with pollen extracts and extracts of other inhalants. In patients with seasonal allergic coryza, with a definite history of food sensitivity, and in all patients who have perennial symptoms, it is wise to test with foods and with extracts of general inhalants and pollens, and to treat as indicated.

207 Doctors Building

USE OF CORTISONE AND ACTH IN THE MANAGEMENT OF NASAL ALLERGY

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DURING the past two years we have treated twelve patients suffering from nasal allergy with cortisone or adrenocorticotropic hormone (ACTH). These patients ranged in age from twenty-six to sixty years. The cortisone was given intramuscularly or orally in doses of 50 to 200 mg daily for six to twenty-one days. The ACTH was given in varying doses which did not exceed 25 mg every six hours for two to fifteen days.

Seven patients were afflicted with hay fever due to sensitivity to pollen of ragweed. Six were given cortisone and two ACTH. One patient received cortisone the first year of our study and ACTH the next. Another patient received cortisone both years. The symptoms of hay fever were well developed each year before medication was started.

In order to lessen the chance for error, the investigation of four of these seven patients with hay fever was set up as follows: Over a four-week period which started late in August, each patient received a daily injection into the gluteal muscles. The material injected was a suspension of 100 mg of either cortisone or cholesterol. In suspension, these substances are identical in gross appearance, and they were dispensed from containers labeled by code number only. Thus, during the month when the study was being conducted and the results recorded, neither the patients nor the physicians knew whether control or test medication was being injected on any given day. Each patient was observed daily by internist and otorhinologist. The presence or absence of asthma and the amount and severity of hay fever, if any, noted in the previous twenty-four hours were recorded. With respect to hay fever, the degree of severity was graded on the basis of 1 to 4; 1 indicated minimal and 4 maximal difficulty. The appearance of the intranasal mucosa was studied daily especially for changes in the degree of pallor, edema, and moisture.

When the study had been completed and all data recorded and analyzed, then the preparation which had been given to each patient on every day of the study was disclosed to us. In no instance was the same substance given for a period shorter than six consecutive days. By this procedure, errors in interpretation of results, due to delayed absorption of cortisone, were minimized.

Two patients with hay fever were given known cortisone throughout

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TABLE I. VASOMOTOR RHINITIS AND HAY FEVER

	Cortisone	ACTH	Total patients treated
Hay fever			
Patients treated	6*	2*	7
Relief during treatment:			
Moderate to marked	5		
Little	1		
Slight to moderate relief with 2nd and 3rd series of 3 courses		1	
Complete relief with each of 2 courses		1	
Vasomotor rhinitis			
Patients treated	3	2	5
Relief: moderate to marked for 3 days to 5 weeks	3	2	

*One patient received courses of both cortisone and ACTH.

the hay fever season. They were observed daily and their symptoms evaluated as in the case of the patients receiving unknown material.

The results following the use of cortisone may be summarized as follows: Moderate to marked symptomatic relief of the hay fever was noted in five cases. This relief was confined to the period during which the cortisone was given. The symptoms of hay fever would recur two to three days after administration of cortisone was stopped. This slight carry-over of relief into the control period we believe was due to delay in absorption of the cortisone injected. One patient noted little if any relief. We believe that dosage was inadequate in this case.

Of the two patients who received ACTH for hay fever, one was remarkably relieved for a ten-day period following a course of treatment lasting forty-eight hours. When her symptoms recurred, the treatment was repeated with the same result. She had no recurrence for the remainder of the season. The other patient noted slight to moderate symptomatic relief after the second and third of three courses of treatment given at intervals of five days.

Five patients were afflicted with vasomotor rhinitis. The symptoms of each of these had been severe and continuous for one to twenty-eight years. Nasal polyps were present in three instances and had been removed repeatedly in two. Three patients were given ACTH and two cortisone. All reported marked symptomatic relief which was noted a few hours to three days after the medication was started and continued for a few days to five weeks after the medication was discontinued. Nasal polyps were observed to shrink to 50 per cent of their original size while patients were receiving these hormones. Results of the whole study are summarized in Table I.

SUMMARY

The administration of cortisone and ACTH to our patients afflicted with nasal allergy has been followed by appreciable symptomatic relief in most instances. The duration of this beneficial effect has varied from a few

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MISCELLANEOUS INHALANTS AND MOLDS

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MANY non-pollen inhalant substances frequently cause nasal allergy. A complete enumeration of such allergens would be impossible, for new ones are being reported constantly. For practical purposes, however, a condensed listing of miscellaneous inhalants, as they are frequently called, could be made under the headings of various environmental and occupational dusts, animal danders and hairs, certain ingredients of insecticides and cosmetics, and seed particles. As to whether molds should be included in this category is debatable, and certainly would depend on one's enthusiasm and interest in molds; these allergens, however, complete the spectrum of non-pollen inhalant substances and therefore will be included in the present discussion.

No definite statement can be made incriminating allergens in this category in the etiology of erratic, distinctly seasonal, or perennial nasal allergy. Any one of the substances under the proper conditions of exposure can be responsible for almost any type of periodic or continued symptoms. It becomes a matter of considerable importance, therefore, to develop evidence of contact in each patient's clinical history and to correlate such facts with skin test data in order for the latter to assume significance. Such correlation may proceed in either direction. Thus, following a careful evaluation of the patient's occupation, habits, environment, and time distribution of symptoms, the suspected allergens may be tested. Or, following clear-cut tests, the history may be reinvestigated, often with clinching additional evidence. In the following remarks, significant facts relative to distribution and particular time or place of contact will be emphasized.

DUSTS

House Dust.—House dust is by far the most widely distributed allergen of the miscellaneous inhalant group. The allergenic factor apparently is formed as a decomposition product of cellulose, particularly cotton. Lint from mattresses, bed covers, upholstered furniture, draperies, or even stored clothing is therefore high in dust allergen. Furthermore, house dust seems to vary noticeably with geographic location, being most potent in warm, humid areas and less allergenic in arid regions. House dust frequently contains other potent allergens such as animal dander, feathers, or even various molds, and in proportion to the content of these sub-

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stances, it varies to some extent in specificity. For practical purposes in obtaining representative house dust for extraction, the author keeps a large box in the office where vacuum cleaner samples collected by individual patients are constantly pooled. House dust is a perennial allergen, but because of impaired ventilation, as well as the increased use of bed covers, it is much higher in concentration in the winter months. Thus, house dust can cause perennial respiratory allergy in more sensitive patients or when its control is not adequate; otherwise, it assumes clinical significance chiefly from early fall to late spring.

Special Dusts.—Dust from stored grain and hay, feed stores, cotton gins, woodworking establishments, et cetera, frequently causes nasal allergies. Farmers or others who contact such dusts constantly may have perennial symptoms or they may be bothered only at such times as they work in the dusts. Usually, special antigens should be prepared from the dusts in question for diagnosis and treatment.

ANIMAL DANDERS AND HAIR

In some animals epithelial scales or danders are produced in large quantities and are potent allergic offenders; in other animals such as cats and rabbits, the dander is absent or negligible and the hairs contain the allergenic properties. Antigens prepared from animal emanations, particularly from the danders, are extremely potent and must be used with great caution in testing and treatment.

Dog Dander.—Dog dander has an obvious source. A dog in the house only occasionally may distribute enough dander to cause symptoms even after the animal has been left outside for several days or weeks. Dog dander is usually a perennial allergen, although it may be contacted only sporadically, such as on visiting in a home where dogs are permitted. Rarely, dog dander may cause definite seasonal symptoms, as during summer vacations in a home where dogs are kept, or in the case of a bird hunter who contacts his dogs only in hunting season.

Cat Hair.—Cat hair accounts for perennial, sporadic or at times seasonal symptoms as in the case of dog dander. Sensitization to cats often exists to such high degree that visiting in a home where a cat has been several months previously, will cause severe clinical symptoms. Persons sensitive to cat hair almost invariably have trouble at the zoo when they are exposed to other animals of the cat family. Cat-sensitive individuals usually require hyposensitization, particularly if they expect to visit away from home.

Horse and Cattle Dander.—Horse and cattle danders may account for severe sporadic or even perennial symptoms in farmers or others frequently exposed to the animals. Horse sensitivity is particularly to be sus-

pected in children experiencing symptoms at summer camps. The short body hair of both horses and cattle, along with adhering danders, is frequently used in furniture upholstery and in under-rug pads; in such concealed places it may give rise to perennial symptoms.

Feathers.—Chicken, duck or goose feathers are at times definite causes of respiratory allergy. On theoretical grounds at least the sensitization may be species specific, but ordinarily individuals sensitive to feathers from one species of fowl have trouble from contact with other species. Feathers seem most allergenic when they are contacted in pillows or mattresses; furthermore, extracts of such old feathers react by test more often than extracts of fresh feathers. This fact brings up the question that such old feathers undergo some sort of decomposition and actually give dust reactions, a theory further substantiated by the frequent occurrence of dust reactions in so-called feather-sensitive individuals.

Rabbit Hair.—Rabbit hair encountered in the Easter bunny or on visits to rabbit hutches is occasionally a significant allergen. Rabbit hair is also encountered as decorations on children's toys, in cheap fur pieces, and in "angora" yarns used in knitting sweaters and other wearing apparel.

Other Animal Hairs.—Other animal epithelia such as mohair (goat), wool (sheep), and hog dander may cause nasal allergy, but the incidence is probably low and the source is usually obvious. In the opinion of the author, wool as an inhalant allergen is often overemphasized. The hairs from such animals as guinea pigs and rats may occasionally cause trouble in laboratory workers, or in children who keep the animals as pets. Hyposensitization may be worthwhile when avoidance is impossible.

The pelts of many species of fur-bearing animals may cause nasal allergy, particularly among workers who process the products. On the other hand, the finished furs are usually so thoroughly cleaned that the dander and loose hairs are adequately removed. The question always arises as to whether dyes in finished furs might not be responsible for occasional inhalant symptoms. Fur sensitization is usually best treated by avoidance. The author cannot recall a single instance in which injections of fur extracts have been effective.

INSECTICIDES

Insecticide powders and sprays frequently cause respiratory allergies, or nonspecific chemical or physical irritation of the respiratory passages. Pyrethrum prepared from ground chrysanthemum flowers is used either in powdered form or as an extract in many insecticides. Pyrethrum often causes hay fever in ragweed-sensitive individuals through the botanical relationship between chrysanthemum and ragweeds. Other vegetable substances such as derris root are occasionally used in insecticides. Most present-day insecticide powders and sprays contain

even more complex chemical substances, and the list is constantly being extended. The many insecticide chemicals are frequently irritants, but rarely they seem to cause true allergic symptoms. The only treatment is avoidance.

COSMETICS

Orris root was formerly used in the perfume and cosmetic industry as a fixative. It is not in common use in most cosmetics at the present time because the manufacturers have learned that cosmetics containing orris root have long since become unpopular. It may still occur, however, in some cosmetics and particularly in sachet powders. Apparently, various odors cause allergic-like symptoms in some individuals; it is impossible to say whether such symptoms are truly allergic.

SEEDS

Seeds are extremely allergenic. Fortunately, whole seeds do not ordinarily produce a great amount of finely divided particles for air dissemination; however, contact in closed places where large quantities of seeds are being manipulated, such as in cleaning operations, may permit relatively heavy contact through the respiratory tract. It must be remembered in this connection, furthermore, that seeds quite frequently are parasitized by molds. On the other hand, various industrial operations involving grinding and crushing seeds produce an enormous amount of highly allergenic dust. Crushed flaxseed is often used in mixed poultry feed, and flaxseed meal is sometimes used in poultices—in one instance, by one of the author's flaxseed-sensitive patients for symptomatic relief during an asthmatic attack!!! Cottonseed meal is used in cattle feed mixtures and as fertilizer. Patients are occasionally sensitive to wheat flour as an inhalant but can ingest wheat products without trouble. Seed antigens are extremely potent and should be used with the greatest caution in testing and treatment.

MOLDS

Mold fungi may be suspected as causes of allergy when they reach a sensitive patient from without, or when they are growing somewhere within his body. The latter consideration deals essentially with the well-known pathogenic forms of Trichophyton and Monilia groups and need only be mentioned briefly here. Furthermore, the pathogenic fungi are usually more concerned in dermatologic allergic conditions and only seldom cause symptoms of nasal allergy, although asthma, vasomotor rhinitis, and urticaria may at times seem to be due to allergens elaborated by these species.

The following remarks will be devoted to the more common air-borne

molds which cause respiratory allergy by simple inhalation just as do pollens and other inhalants.

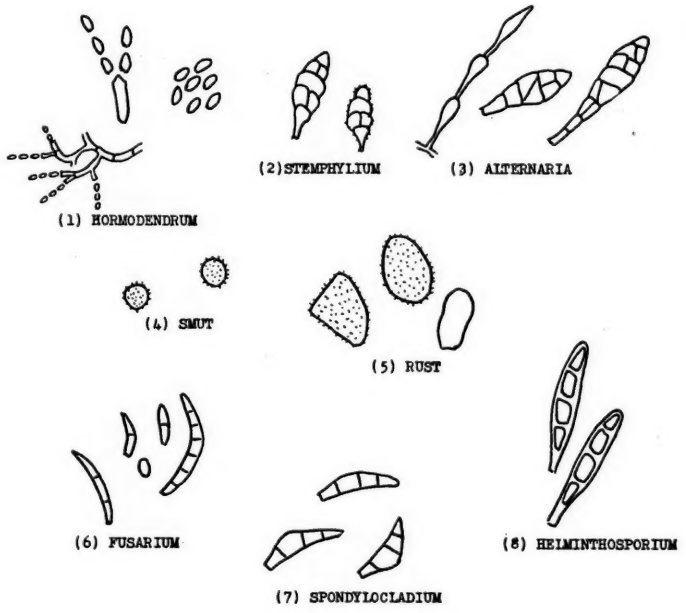

Fig. 1. Approximate spore sizes in microns. (1) 3-6x2-3. (2) 25-40x16-20. (3) 30-36x14-15. (4) 8-11x5-9. (5) 13-21x23-26. (6) 12-29x3-4. (7) 25-30x12-15. (8) 22-26x9-11.

Sources.—Soil is the most universal habitat for molds. Soil fungi play a prominent part in the decomposition of proteins and other organic matter, returned to the soil in plant residues. Most of the common forms such as Penicillium, Aspergillus, Fusarium, Alternaria, Helminthosporium, Hormodendrum, and the Mucorales are thus widely distributed.

Mildew of textiles is generally due to various species of Aspergillus or Penicillium introduced in raw material during process of manufacture or acquired in exposure to air in damp environments: awnings, tents, draperies, window shades, wallpaper and the canvas beneath it, et cetera, may furnish much mold growth in damp districts.

Upholstered furniture, especially that containing kapok, and mattresses which may contain raw cotton, furnish excellent substrata for mold growth. Colored stains in raw cotton may be due to Fusarium, Cladosporium, or Aspergillus; tethering or loss of strength to *Aspergillus fumigatus, Cladosporium herbarium,* Stemphylium, Chaetomium, and

Penicillium. Since either of these phenomena cheapens the quality of the cotton, it seems logical that the cheaper grades of cotton generally used in bedding or upholstery may contain much infested material from the raw product.

Wool may be a source of Penicillium and Aspergillus. Manila hemp may deteriorate from *Aspergillus fumigatus, A. flavus,* and *A. niger.*

Common bread mold, *Monilia sitophila,* occurs in bakeries and in many homes; it produces very fine spores in abundance and may be a potent allergen.

Luggage, shoes, gloves, and other leather articles frequently become molded in damp climates.

Citrus fruits, cured hams, and other foods may become heavily molded and produce great numbers of spores. *Penicillium italicum, P. digitatum, P. expansum,* and *P. notatum* are commonly encountered.

Plants may be infected with parasitic fungi. These may be important in the agricultural areas, especially in the major grain belts, and certain urban districts where much grain is handled, as in grain elevators, flour and feed mills, et cetera.

Methods of Air Analysis for Mold Identification.—A. Pollen Slide Method. Unfortunately only a very few forms can be recognized by spores or mycelial fragments. Figure 1 is a pen sketch showing forms that may be recognized. High-power verification is often necessary, especially for Hormodendrum which is usually identified in characteristic spore clumps. The rusts and smuts can be recognized as such, and species identification is facilitated by experience. Since rusts are obligate parasites and the smuts grow atypically in culture, their identity depends entirely on use of the slide method.

B. Culture Plate Method. This method of necessity has been the basis of most studies of air-borne molds. Since identification depends on specialized training, the allergist usually must work in co-operation with someone proficient in mycological technique. He may, however, prepare and expose culture plates in any particular environment such as a cellar, a patient's room, et cetera, or he may prefer to study the outside air, in which case he would make exposures from the roof of some isolated high building. Culture media may be ordinary Sabouraud's agar; a special wort agar may be obtained from the Difco Company in dehydrated form. The plates may be exposed for any convenient length of time; some investigators have preferred fifteen minutes, but in our studies a two-minute exposure has been found preferable, since with the shorter exposure overgrowth from too many colonies is minimized. It is imperative that exposed plates be wrapped in sterile paper and transported to the mycologist immediately after exposure, especially if they must be sent by parcel post, so that all growth features may be observed before overgrowth occurs.

Geographic Distribution and Seasonal Incidence of Dominant Forms.—Geographic distribution and seasonal incidence of dominant forms as determined by the plate method in surveys made by the Association of Allergists for Mycological Investigations in central and southwestern United States[1,2] and by other surveys:

Alternaria seemed to be of more frequent occurrence than any other genus. In southern areas it occurred perennially; in the north it was greatly reduced in the winter but was increased to produce a definite "season" in the warmer months with highest count in the fall. It may, therefore, be an important offender between the spring and fall pollen seasons, and may complicate the ragweed season especially.

Hormodendrum ranked next to Alternaria in high counts and frequency of occurrence. Except in the north during the winter months it was found more or less consistently. In the south it seemed more prevalent in the winter, spring and fall; in the north it was highest in late spring and fall, being slightly reduced through the summer.

Helminthosporium and Spondylocladium occurred in the north only in the summer, and in the south in spring, summer and fall. Counts were lower than Alternaria and Hormodendrum.

Aspergillus and Penicillium were widely distributed but counts were generally low; seasonal or geographic differences were not suggested.

Fusarium was widely distributed but counts were low; it was encountered more frequently in the south than in the north, suggesting seasonal factors.

Mucorales, represented by Rhizopus, Mucor and Absidia: counts were uniformly low, occurrence was sporadic; no seasonal or regional trends were suggested.

"Sterile mycelium" (colonies which do not develop spores or other distinguishing characteristics; may include mushroom mycelium or vegetative mycelium of certain plant pathogens): counts were low and no seasonal or regional incidence prevailed.

Species with "bodies," as pycnidia and perithecia, include Phoma and Chaetomium. Occurrence was sporadic and the counts were low. (Phoma was observed at Decatur, Illinois, regularly from April through November in 1943.)

Pullularia, as *Pullularia pullulans,* occurred in unpredictable "showers," with relatively high counts. Mycogone generally occurred sporadically with relatively low counts.

The above groups are those found with sufficient regularity to be called dominant. Various other molds have been encountered, but less frequently, over wide areas.

*Practical Grouping of Molds for Skin Testing.**

A. *Pathogenic*

Trichophyton
Monilia albicans
0.05 cc intradermally in dermatological cases and watch for delayed reactions.

B. *Air-Borne*

In the following arrangements the common air-borne molds are listed according to their botanical relationships. This classification could be used in selecting a mold set for skin testing.

Phycomycetes

Mucoraceae:
Rhizopus spp.
R. nigricans
Absidia spp.
Mucor spp.

Ascomycetes

(1) Saccharomycetaceae:
Sacc. cerevisiae
(Brewer's yeast)
(2) Torulaceae:
Torula spp.
(3) Chaetomiaceae:
Chaetomium spp.
(4) Powdery mildews

Basidiomycetes

(1) Hemibasidiomycetes (smuts):
Ustilago (loose smuts—wheat, barley; covered smut—barley; "smut"—corn, oats, millet and grass)
Urocystis (flag smut—wheat, rye, onion)
Tilletia (stinking smut or bunt—wheat; black smut—rice)
Sorosporium (Ustilago) (head smut—corn, sorghum)
Sphacelotheca (covered kernel smut—sorghums; Johnson grass; loose kernel smut—sorghums)
Ustilaginoidea (green smut—rice)

(2) Protobasidiomycetes (rusts)
Puccinia graminis
Uredospore (red rust on wheat leaf)
Teleutospore (black rust on wheat stem)
Basidiospore (in soil, on stubble and straw)
Aecidiospore } on barberry leaf
Pycnidiospore }

(3) Eubasidiomycetes (fleshy fungi)
Agaricus (Psalliota)
Field mushroom
Calvatia
Puff ball
Polyporus
Shelf fungi

These forms are of local occurrence only; the author uses them because their spores are easily obtained, and in the hope that generic relationship might associate reactions with rust or smut sensitivity particularly since the latter antigens are not easily obtained.

*The author is indebted to Marie B. Morrow, Ph.D., Department of Botany, The University of Texas, Austin, Texas, for this classification and listing of molds.

Fungi Imperfecti
Sphaeropsidales

(1) Sphaerioidaceae
Phoma spp.
Chaetomella spp.
Other pycnidial spp.

Hyphomycetales

(2) Moniliaceae
Monilia
M. sitophila
(M. albicans—candicans: M. albicans group pathogenic, see pathogenic molds above)
Trichoderma
T. viride (lignorum)
Aspergillus
A. glaucus group (green)
A. fumigatus (often pathogenic) (blue-green; aqua)
A. nidulans (green; purple ascospores)
A. sydowi (blue-green becoming dark tan-brown)
A. terreus
A. luchuensis (deep reddish-brown)
A. niger group (deep yellowish-brown)
Penicillium
P. notatum
P. biforme
P. carmino-violaceum
P. luteum
P. chrysogenum
Penicillium monoverticillate group
Paecilomyces
Paec. variotii
Gliocladium
Glio. penicillioides
Botrytis
Bot. cinerea
Mycogone
Mycogone spp.

(3) Dematiaceae
Nigrosporum (Basisporium)
N. sphaerica (B. gallarum)
Pullularia (Dematium)
Pull. pullulans
Hormodendrum (Cladosporium)
H. cladosporioides
H. hordei
Helminthosporium (Curvularia)
H. interseminatum
Spondylocladium (Curvularia)
Curvularia
C. spicifera
C. trifolii
Stemphylium
S. botryosum
Alternaria
A. tenuis

(4) Tuberculariaceae
Fusarium (Hymenula)
Fusarium spp.

Practical Instructions for Mold-Sensitive Patients.—Precautions against house dust, including the use of impervious envelopes on mattresses and pillows, will usually reduce immediate or indoor mold contact. In areas

of high humidity, special care must be taken to see that shoes, gloves, suitcases, clothing, et cetera, are not allowed to become molded in damp storage closets; an electric light kept burning in a closed closet is very helpful for this purpose. Upstairs apartments are often much drier and therefore less conducive to mold growth than are downstairs rooms. Even in dry climates basement rooms, especially those containing cement floors and walls, are quite likely to be so damp that mold growth is difficult to control. Occasionally insulation on air-conditioning equipment or refrigeration installations become so wet that abundant mold growth takes place.

Mold-sensitive patients should always be instructed to avoid grain-harvesting or grain-handling operations, and contact with hay stacks and feed barns. Quite often the dead stubble in cut-over grain fields, as well as dead and decaying vegetation in general, such as occurs after the first killing frost, produces heavy mold growth, particularly of Alternaria and other species of the dematiaceae. Travel in rural areas, especially on dry, windy days, during such periods may prove hazardous from the standpoint of mold allergy.

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USE OF CORTISONE AND ACTH IN THE MANAGEMENT OF NASAL ALLERGY

(Continued from Page 574)

days to five weeks after administration of the hormones was discontinued. The mechanism by which these substances ameliorate the symptoms of nasal allergy is not established, but it may be related to the known anti-hyaluronidase effect of 17-hydroxy-11-dehydrocorticosterone.

The administration of cortisone and ACTH in the dosage and for the duration employed has not been followed by any undesirable symptoms or manifestations.

We believe, therefore, that these substances, although possessed of no demonstrable curative value, have a place in the symptomatic treatment of patients afflicted with nasal allergy who have not responded well to other orthodox therapeutic measures.

SURGICAL MANAGEMENT OF NASAL AND SINUS ALLERGY

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SUCCESSFUL management of allergic rhinosinusitis is contingent upon close co-operation between the allergist and the rhinologist. It is true that many cases of nasal allergy respond satisfactorily to the control of the allergy alone, but it is also true that individuals suffering from polyposis are definitely rhinologic cases and that they will not be relieved of their symptoms until these conditions receive proper attention. Rhinologists are commonly consulted by patients for relief of what they think is sinusitis. The sinus involvement, if any, is often negligible compared to the real condition of nasal allergy causing the patient's complaints.

One of the great mistakes of rhinology is failure on the part of the rhinologist to recognize allergy in these patients. They are often treated by ineffective sprays, packs, or surgical procedures, while the cause of the symptoms is overlooked or touched upon ineffectively. Equally to be deplored is the custom of some allergists of withholding nasal examination and therapy from patients suffering from a nose full of polyps and chronic suppurative sinusitis.

Otolaryngologists have been slow in recognizing the importance of allergy to their specialty, yet it has been generally estimated that a majority of their cases involving the ear, nose and throat are on an allergic basis. This is especially applicable to the nasal cases because in these the nasal mucosa is constantly exposed to the airborne antigens.

Otolaryngologists in order to properly handle these cases should acquaint themselves with the signs and symptoms which point to the diagnosis of allergy. They then, when confronted with such cases, should at the outset see that the patients receive an adequate allergy survey and are placed under proper allergy management. Following this, attention is directed to the nose and sinuses. Polyps are removed, sinuses are irrigated as indicated, and other nasal conditions such as septal deviations and spurs are treated as they present themselves.

POLYPS

Nasal polyps are of considerable clinical importance not only because they produce the annoying symptoms of nasal obstruction but because of their presence in or near the drainage areas of the sinuses they contribute

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much toward the inception and maintenance of attacks of sinusitis. Another item of major importance is the fact that many cases of malignancies of the nose and sinuses have a history of several months or years of nasal polyposis.

Polyps develop as a result of irritation of nasal or sinus mucosa. The irritant may be an allergen, a pathogen, or a toxic exudate from a draining sinusitis.

The histopathology is essentially that of edematous respiratory epithelium. Should the growth be allergenic, a preponderance of eosinophils is present in the mucosa. The actual polyp develops from a prolapse of overloaded mucosa into the nasal or sinus cavities.

Points of Origin.—Contrary to the generally accepted belief, the common site of origin of nasal polyps is not in the ethmoid cells. They arise rather from the exposed areas of the middle meatus such as the crest of the uncinate process, the margins of the maxillary ostium, and the anterior surface of the ethmoid bulla, and are as a rule easily accessible for removal by means of a wire snare.

Polyps tend to recur after removal unless the causative factors have been eliminated. In cases of chronic untreated sinusitis or uncontrolled allergy, polyps invariably reappear to block the nasal passages and sinus drainage within a few weeks or months after what has appeared to be complete removal.

The management of chronic nasal polyposis has been greatly enhanced, however, by the advent of better understanding of nasal allergy and with the improvement in our management of chronic sinusitis. Early in the history of rhinology and at periods during recent years the established custom was removal not only of the new growths but all structures from which they might arise. Many surgeons felt and still do that proper handling of the condition called for intranasal exenteration of the entire ethmoid labyrinth of cells, and others employed the complete external pansinus operation which they thought was the answer to the recurring polyp problem. The adoption of these procedures is based on the premise that the polyps for the most part have their roots in the ethmoid cells. Since this is a false premise it is easily understandable why ethmoid exenteration and the multiple sinus operation have resulted largely in failure.

Up to the present time no highly efficient method or technique has been developed for the complete and permanent eradication of nasal polyps. It has been established, however, that modern conservative measures are far more effective than the radical procedures of the past. With the simpler methods all patients are made more comfortable and may attain permanent relief. The growths are removed as a simple office procedure, and in many cases, especially those under proper allergy management, there is no recurrence.

SINUSITIS

Treatment of the sinuses is carried out whether the involvement be purely allergic in nature characterized by a pale exudate or of a purulent type with yellow or greenish discharge. The sinuses are irrigated periodically, and measures are adopted for the improvement of sinus drainage. Polyps are removed and blocking middle turbinates are dealt with. Extra drainage openings (windows) are inserted when required. All efforts are concentrated on bringing about an improvement in the allergy, for it may be assumed that in most cases the edema of the allergy has contributed much toward the maintenance of the infection in the sinuses and that the sinuses will be more amenable to treatment as the allergy is placed more nearly under control.

The radical surgical procedures of the past on allergic cases have been largely discontinued, for it has been determined that whatever relief was gained from these was temporary only. This is understandable when it is realized that the main cause of trouble, allergy, was in no way helped by the procedures. Allergic membranes were removed, but eventually these were replaced by membranes also allergic and the pathologic condition was resumed.

ASTHMA

The same applies to the radical surgical operations advocated for the cure of asthma. A few years ago I had an opportunity to study the records of a large series of patients who had been subjected to the complete external ethmofrontal sphenoidectomy. I examined the slides made from the removed tissues, the preoperative record, and the postoperative course. All received temporary relief following this mutilating procedure. In some the relief was of six weeks' duration, and some were asthma-free for two years. All, however, eventually had a return of the asthma, and, in most, the symptoms were more pronounced than they had been preoperatively; in many there was an added purulent sinusitis, a condition from which they had been entirely free before the institution of the surgical procedures.

SUMMARY

Successful management of allergic rhinosinusitis is contingent upon close co-operation between the allergist and rhinologist.

Nasal polyps definitely are problems of the rhinologist. On occasions these growths recede and this is more likely to happen when the patient's allergy or sinusitis is under control. The tendency in polyposis, however, is toward continued growth and recurrence even after what has been thought to be complete removal. Nasal polyps should be removed when they are of such a nature as to obstruct breathing or sinus drainage. Extensive surgical procedures to accomplish this are seldom indicated

(Continued on Page 702)

OBSERVATIONS ON THE USE OF ACTH AND CORTISONE IN THE TREATMENT OF ASTHMA, HAY FEVER, AND OTHER ALLERGIC CONDITIONS

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EARLY reports[1,12] which described the striking improvement occurring in certain cases of allergic disease under the influence of ACTH and cortisone have been adequately confirmed by many subsequent observers. It has become apparent, however, even in the relatively brief period since these hormones became available for general use, that a wide variation in individual response may be anticipated in allergic-type reactions. A dramatic improvement may occur in some instances, while other apparently similar cases are not benefited. At this time the indications for ACTH or cortisone therapy in allergic diseases and the limitations of their usefulness are not definitely established. Considerably greater understanding of the basic mechanisms by which increased adrenal cortical function influences allergic reactions is required before such principles can become more fully crystallized.

The present report summarizes observations made in a group of patients with asthma, hay fever, and other allergic diseases who received ACTH or some form of cortisone during the past year. In most cases a sufficient period of time has elapsed to make an evaluation of the effect of a single course of such treatment. In a number of instances it is also possible to summarize the effects of repeated courses with one or both of the hormones, and to mention preliminary efforts to prolong remissions by the continued administration of smaller amounts after an intensive course has been given.

TREATMENT OF BRONCHIAL ASTHMA (TABLE 1)

Earlier observers[14] have included severe asthmatic states among those diseases in which ACTH and cortisone may be found most useful. The cases of asthma included in the present study may be divided into two general groups: those treated in the hospital with ACTH or cortisone by injection, and those receiving oral cortisone on an ambulatory basis. The cause of asthma in some cases could be related wholly to extrinsic allergic factors, while in others no definite environmental or dietary sensitizations could be established. The etiology in the majority of cases could be considered a combination of extrinsic and intrinsic factors. In appraising the

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TABLE I. USE OF ACTH AND CORTISONE IN ASTHMA

Hormone	Route	Initial Daily Dose —mg.	Ambulant or Hospital	Number of Cases	Results		
					Good	Fair	Poor
ACTH	I.M.	100	Hospital	10	6	2	2
Cortisone	I.M.	300	Hospital	11	4	4	3
Cortisone	Oral	100–200	Ambulant	20	13	3	4

effects of ACTH and cortisone in these patients, no definite relationship could be established between the etiologic classification of asthma and the therapeutic response noted.

Effect in Hospitalized Patients.—Each patient who received ACTH or cortisone by injection was hospitalized in severe status asthmaticus. Symptomatic measures such as aminophylline, intravenous fluids, epinephrine, iodides, helium and oxygen inhalations were instituted immediately upon admission, if required, and continued as necessary during the course of the hospital stay. A period of twenty-four hours or more usually elapsed between the time of admission to the hospital and the institution of ACTH or cortisone therapy. Routine laboratory examinations prior to hormone treatment included red, white and differential blood count, urinalysis, total blood eosinophils, blood sugar, nonprotein nitrogen, chlorides, sodium, and potassium. Total blood eosinophils were repeated daily, and other laboratory procedures were rechecked at some period during hospitalization. Daily weights and blood pressures were recorded in each instance, and diets low in sodium with supplements of potassium salts were usually given.

In evaluating the results of ACTH or cortisone therapy, all subjective and objective data were utilized. It is realized that the hospitalization procedure itself, apart from the symptomatic measures which are there more readily administerable, may frequently exert a beneficial effect on the patient with severe asthma. Alteration of environmental sensitization factors and the relief of marked apprehension may contribute to the patient's improvement. The effects of hormone therapy, however, were often so prompt and dramatic that there remains little question that symptoms in these cases were influenced by its use.

Those who were considered to have achieved a good result from ACTH or cortisone began to improve shortly after hormone therapy was instituted and rapidly progressed to a point where all subjective signs and objective findings of asthma completely disappeared. In other cases where improvement was slower or incomplete, the influence of the hormone in producing these changes was perhaps more difficult to assess.

The Use of ACTH (Table II).—Among ten hospitalized patients ranging in age from twenty-six to sixty-five years with severe asthma of two to thirty years' duration who were given an initial course of ACTH, six

TABLE II. THE EFFECT OF AN INITIAL COURSE OF ACTH IN CASES OF BRONCHIAL ASTHMA

Case	Age	Sex	Duration of Asthma —years	Etiologic Factors*	ACTH		Clinical Effect	Remission —days
					Total Dose —mg.	Days of Therapy		
1	65	F	15	E & I	700	12	Good	23
2	55	M	15	E & I	690	12	Good	21
3	52	M	14	E & I	600	6	Poor	—
4	30	F	25	E & I	615	10	Good	7
5	52	F	2	I	870	13	Poor	—
6	49	F	15	E & I	710	13	Fair	12
7	32	M	25	E	700	11	Good	14
8	27	F	21	E	620	10	Good	19
9	26	F	16	E & I	680	10	Good	15
10	63	M	30	E & I	620	12	Fair	7

*E—Extrinsic
I—Intrinsic

achieved a prompt and dramatic improvement which could be attributed to the influence of the hormone, two were improved but not completely relieved, while two others did not respond favorably. The initial daily dose of ACTH in each instance was 100 mg given in 25 mg amounts at six-hour intervals. In six patients who were greatly benefited by such therapy marked improvement was present after twenty-four to thirty-six hours, and complete remission was attained at the end of the fifth day. Moderate improvement which could be related to ACTH was noted in two patients. In two remaining cases there was no apparent benefit from such treatment. One of these failed to improve during a six-day period and was immediately transferred to cortisone. A somewhat better response occurred after treatment with the latter substance. Another patient who was unimproved while receiving ACTH received cortisone during a later hospitalization also without effect.

Depending on the clinical response which ensued, the initial dose of ACTH was gradually reduced after three to six days of therapy. Total doses of the hormone ranged from 600 to 870 mg administered over a period of six to thirteen days. The average total dose was 680 mg given for 10.9 days.

The periods of remission in eight cases who were benefited lasted from seven to twenty-three days, and the severity of asthma which recurred was at least equivalent to the original symptoms. There appeared to be no direct relationship between the total amount of ACTH administered and the clinical results obtained, or to the duration of the remissions experienced. Administration of 25 mg two or three times weekly in two patients after hospitalization did not prevent the recurrence of symptoms.

The Use of Cortisone (Table III).—In eleven patients who were hospitalized for an initial course of cortisone, 100 mg was administered every eight hours for three doses, followed by 100 mg every twelve hours for three to eight days depending on clinical response. After this the dose was progressively reduced. The immediate favorable response which

TABLE III. THE EFFECT OF AN INITIAL COURSE OF PARENTERAL CORTISONE IN CASES OF BRONCHIAL ASTHMA

Case	Age	Sex	Duration of Asthma —years	Etiologic Factors*	Cortisone Total Dose —mg.	Days of Therapy	Clinical Effect	Remission —days
1	65	F	15	E & I	1200	10	Good	7
2	55	M	15	E & I	1300	11	Good	14
3	52	M	14	E & I	1450	13	Fair	42
4	30	F	25	E & I	1100	11	Good	16
5	52	F	2	I	1450	13	Poor	—
6	49	F	15	E & I	2225	16	Fair	7
17	32	M	22	E	1300	12	Poor	—
18	47	M	30	E & I	1400	15	Good	36
19	50	M	25	E & I	1475	10	Fair	17
20	32	F	25	E	1200	11	Fair	12
21	29	F	16	E & I	1350	12	Poor	—

*E—Extrinsic
I—Intrinsic

occurred from the use of cortisone was somewhat slower in onset than that observed following ACTH. In four patients definite subjective and objective improvement was present after three days of therapy, progressing to complete remission at the end of six days of treatment. The asthma in four other patients was favorably affected but was not completely relieved. The remaining three patients were not benefited by such therapy.

The total doses of cortisone ranged from 1,200 to 2,225 mg administered over periods of ten to sixteen days. The average dose in ten patients while hospitalized was 1,300 mg given over a period of 11.7 days, while one patient received 2,225 mg during sixteen days of treatment. Three patients who attained a complete or partial remission in the hospital attributable to cortisone were given no further injections after discharge. In these cases a recurrence of asthma occurred seven to sixteen days later. In four patients who were given 25 mg of cortisone by injection twice weekly following completion of the course in the hospital, severe symptoms recurred fourteen to forty-two days later. It appeared that the remission in two of these cases may have been prolonged by continuation of small amounts after the original intensive course. In one other patient who received 25 mg of oral cortisone daily after discharge, asthma recurred seven days after leaving the hospital.

Effect of Repeated Courses of ACTH and Cortisone (Table IV).—Six patients in the present series with severe chronic asthma were hospitalized on two or more occasions for therapy with either ACTH or cortisone.

Case 1.—A sixty-five-year-old woman, who gave a history of asthma of fifteen years' duration, becoming more severe during the past two years, was hospitalized on four occasions between August 5 and November 7, 1950, receiving three successive courses of ACTH followed by one course of cortisone. Improvement was prompt and remission was complete each time. The duration of the first remission was twenty-three days, the second was sixteen days, and a free period of six days followed the third course of ACTH. Interim injections of 25 mg of ACTH were given twice weekly between the first and second, and second and third courses,

TABLE IV. THE EFFECT OF REPEATED COURSES OF ACTH AND CORTISONE IN ASTHMA

Case	Course No.	Hormone	Interval Between Courses —days	Total Dose —mg.	Days of Therapy	Clinical Effect	Remisson —days
1	1	ACTH	—	700	12	Good	23*
	2	ACTH	27	565	10	Good	16*
	3	ACTH	18	630	10	Good	6
	4	Cortisone (I.M.)	8	1350	16	Good	7
2	1	ACTH	—	690	12	Good	21
	2	Cortisone (oral)	90	900	6	Poor	—
	3	Cortisone (I.M.)	1	1300	11	Good	14*
	4	ACTH	30	740	11	Good	14*
3	1	ACTH	—	600	6	Poor	—
	2	Cortisone (I.M.)	—	1500	9	Fair	42*
	3	ACTH	29	620	10	Poor	—
4	1	Cortisone (I.M.)	—	1100	11	Good	13
	2	ACTH	170	690	10	Good	8
5	1	ACTH	—	870	13	Poor	—
	2	Cortisone (oral)	48	900	6	Poor	—
	3	Cortisone (I.M.)	7	1450	13	Poor	—
6	1	Cortisone (I.M.)	—	2225	16	Fair	7
	2	ACTH	26	710	13	Fair	14*

*Interim injections given during remission period (see text)

while no additional hormone was administered between the third and fourth hospitalizations. The asthma which recurred following each course of ACTH appeared increasingly severe, but response to re-treatment was always good. Cortisone was given during the fourth hospitalization with an equally good clinical improvement, but symptoms recurred seven days after it was discontinued.

Case 2.—A fifty-five-year-old man with severe asthma of nineteen years' duration had a history of repeated hospitalizations for asthma over the past four years. During a period from July 12 to December 24, 1950, he was hospitalized on three occasions for ACTH or cortisone therapy. Following an initial course of ACTH, he was completely relieved for twenty-one days. Next, a course of oral cortisone while ambulatory was not helpful, and he was hospitalized for cortisone by injection. He made a good response to such therapy, but this remission lasted only fourteen days despite 25 mg daily of cortisone during this period. Another course of ACTH was given during the third hospital period and was followed by a complete remission. He continued to receive 20 mg of ACTH daily after discharge, but severe attacks of asthma began to recur fourteen days after leaving the hospital.

Case 3.—A fifty-two-year-old man had a history of severe asthma of fourteen years' duration. During a period from September 17 to December 8, 1950, he was hospitalized twice for ACTH and cortisone treatment. During his first hospitalization he received 100 mg of ACTH for six days without improvement in his asthma or appreciable decline in blood eosinophils. This was immediately followed by a course of cortisone, 1,500 mg being given during the next nine days. He showed moderate improvement during the latter part of his hospital stay, and continued to improve while receiving 25 mg injections of cortisone once or twice weekly on an ambulatory basis. Severe asthma recurred forty-two days later, and increased doses of cortisone not only failed to help but appeared to precipitate acute paroxysms of asthma. Cortisone was stopped suddenly, and he was readmitted to the hospital three days later with symptoms suggesting adrenal insufficiency. ACTH improved

his general condition but produced no dramatic effect in his asthma. A slight reduction in blood eosinophils occurred during this period. At the time of discharge his symptoms were largely controlled with symptomatic drugs. Two days after leaving the hospital he developed a series of severe asthmatic paroxysms associated with short periods of "blacking out" and expired suddenly during a seizure.

Case 4.—A thirty-year-old woman with a history of asthma of approximately twenty years' duration was hospitalized for cortisone therapy in May, 1950, and for ACTH in November, 1950. Both hormones were equally effective in inducing a remission, although symptoms returned a short time later in each instance. In comparison with repeated prior hospitalizations for the same condition, each of which was marked by a stormy course and a prolonged period of convalescence, the use of ACTH and cortisone produced a prompt and dramatic improvement on both occasions.

Case 5.—A fifty-two-year-old housewife had severe asthma of two years' duration. A course of ACTH in October, 1950, was without benefit. An interim course of oral cortisone was not helpful, and a second hospitalization period in December, 1950, during which an intensive course of cortisone by injection was given failed to influence her asthma favorably.

Case 6.—A forty-nine-year-old woman with a history of severe asthma over a period of fifteen years was hospitalized in October, 1950, in severe status asthmaticus. An intensive course of cortisone resulted in moderate improvment which lasted for seven days after discharge from the hospital. Her condition became progressively severe, and rehospitalization was necessary early in December, 1950. A course of ACTH produced a better response than cortisone, and following her discharge from the hospital she received injections of 25 mg ACTH twice weekly. Asthmatic symptoms began to recur twelve days after leaving the hospital, and it was necessary to readmit her two days later.

Effect in Ambulatory Patients.—Twenty patients with severe asthma were given cortisone by oral administration. Thirteen were promptly and completely relieved by such therapy, three appeared to be benefited to a lesser degree, while four others were unimproved. The results of oral cortisone therapy have been reported by us in more detail elsewhere.[6] The hormone was given in the form of 25 mg tablets. Initial daily doses of 100 to 200 mg were usually divided into 25 or 50 mg amounts and administered at four- to eight-hour intervals. A favorable symptomatic response was frequently noted within the first six hours, progressing to complete relief of symptoms by the end of twenty-four to forty-eight hours. Depending on the clinical response, the individual doses were subsequently more widely spaced, being given at twelve- and twenty-four-hour intervals. The period of hormone administration ranged from six to eighteen days, with an average of ten days of treatment. The total dose for a single course averaged 1,000 mg.

The remissions which occurred under the influence of oral cortisone were generally of short duration, symptoms often recurring within a few days after withdrawal, and in some instances when the daily dose was reduced to the level of 25 or 50 mg. Repeated courses of oral

TABLE V. EFFECT OF ACTH AND CORTISONE IN HAY FEVER

Hormone	Route	Initial Daily Dose—mg.	Ambulant or Hospital	Number of Cases	Results		
					Good	Fair	Poor
ACTH	Intramusc.	100	Hospital	3	3	0	0
ACTH	Intramusc.	25	Ambulant	16	1	1	14
Cortisone	Intramusc.	100	Ambulant	5	1	2	2
Cortisone	Oral	150	Ambulant	8	6	0	2

cortisone usually produced the same dramatic improvement, followed by a rapid relapse when the hormone was discontinued. Present efforts with this form of cortisone in asthma are being directed toward prolongation of the remission period by continuing the administration of small amounts over longer periods of time.

TREATMENT OF HAY FEVER (TABLE V)

During the 1950 ragweed pollinating season the effects of ACTH and parenteral and oral cortisone were noted in hospitalized and ambulatory hay fever patients. Each of the subjects selected for hormone therapy was specifically sensitive to ragweed pollen and presented classical symptoms of pollinosis occurring concomitantly with the appearance of pollen in the air. The majority had not received adequate hyposensitization therapy before treatment with ACTH or cortisone, and were having active difficulty with little or no benefit accruing from antihistaminic or other symptomatic medications at the time hormone therapy was instituted. In making an evaluation of the effect of these agents, symptoms were correlated with the pollen count and atmospheric condition, and comparisons were made with adequate control patients. Placebos were frequently employed in ambulatory patients to verify clinical impressions that the agents used were responsible for any improvement noted.

ACTH in Hospitalized Patients.—Three patients with severe hay fever symptoms were hospitalized for ACTH therapy, and after an initial control period in the hospital of twenty-four to forty-eight hours were started on 25 mg every six hours. Treatment in each case was begun on August 26, at which time the pollen concentration was 187 grains per cubic yard of air. Initial improvement was noted by the end of the first twenty-four hours of therapy, and all three were asymptomatic by August 30, at which time the pollen count had increased to 280 grains. All were discharged on September 2 after having received a total of 485 mg, 420 mg, and 410 mg, respectively. No active hay fever symptoms recurred during the balance of the season in these three cases.

ACTH in Ambulatory Patients.—Sixteen patients received 25 mg of ACTH daily in a single injection for an eight-day period between August 26 and September 2, 1950. A similar group of ten patients received

placebo injections during the same period. On August 26 the pollen concentration was 187 grains, and varied between 108 and 306 during the period of treatment. Fourteen patients did not achieve any benefit which could be definitely attributed to ACTH administration. There was a feeling in some instances that temporary improvement occurred for several hours after each injection, but this could not be confirmed by objective evidence. One other patient who received ACTH was remarkably improved within twelve hours after the first injection, despite an increase in pollen to 306 grains on the following day. The remission in this case persisted during the period of study and the balance of the pollinating season. Another subject appeared to be definitely benefited but not completely relieved after the first two injections of ACTH, and remained so while daily injections were being given. She again experienced acute symptoms six days after such therapy was discontinued, during a period of high pollen concentration from September 8 to 10.

Cortisone by Injection in Ambulatory Patients.—Five patients received injections of cortisone suspension for periods of seven to seventeen days during the height of the ragweed pollinating season. The initial dosage, which in all cases was 100 mg given in a single injection, was administered at daily intervals during the first seven days, and later every second or third day, with gradual reduction in the amount of each injection to 50 and 25 mg. One patient was completely relieved of all symptoms at the end of the third day and continued free during the period of treatment, which was stopped on the seventeenth day. He experienced only minor symptoms during the balance of the season. Two other patients were greatly benefited but not entirely relieved after three days of treatment; however, they relapsed on several occasions when the dose was reduced to 50 mg for a period of forty-eight hours, or when placebo injections were substituted for the daily dose of cortisone over a period of two or more days. The two remaining patients in this group were not relieved while receiving cortisone over a seven- to ten-day period.

Oral Cortisone in Ambulatory Patients.—Oral cortisone was given to eight hay fever sufferers toward the end of the 1950 pollinating season. Treatment was begun on September 9 in this group, at which time the pollen count was 237 grains. On September 10 the concentration of pollen was 230 grains per cubic yard but fell to 40 grains on September 11, and remained low for the balance of the season. The initial dose of cortisone prescribed was 25 mg. every four hours. Six patients reported marked improvement within four to eight hours of the first dose and were almost completely relieved when seen twenty-four hours later. Similar dramatic improvement did not occur during this period in two other patients who received similar amounts of cortisone by mouth, and in a group of control patients. After three days of treatment at this dosage level, the hormone was progressively reduced and discontinued on the tenth

TABLE VI. EFFECT OF ACTH AND CORTISONE IN OTHER ALLERGIC DISEASES

Condition	Hormone	Route	Ambulant or Hospital	No. of Patients	Results		
					Good	Fair	Poor
Atopic dermatitis	ACTH	I.M.	Hospital	2	0	2	0
	Cortisone	I.M.	Hospital	2	0	1	1
	Cortisone	Oral	Ambulant	7	2	3	2
Contact dermatitis	Cortisone	Oral	Ambulant	2	1	1	0
Urticaria and Angioneurotic edema	ACTH	I.M.	Hospital	1	0	0	1
	Cortisone	Oral	Ambulant	4	2	2	0

I.M.—Intramuscular

day. While symptoms did not recur in these patients during and after cortisone therapy, the low pollen concentration makes it difficult to attribute the continued remission to the effects of cortisone. It was felt, however, that the oral cortisone was directly responsible for the prompt initial improvement observed in these six cases.

TREATMENT OF OTHER ALLERGIC CONDITIONS

Atopic Dermatitis.—Seven young adults with extensive eczematous eruptions, which had been present for periods ranging from nine months to eighteen years, were given oral cortisone while ambulatory. Two were markedly benefited, three others showed limited improvement, while in two patients the dermatitis was unaffected by such therapy. The courses of treatment ranged from six to sixteen days, with total doses of 600 to 1,550 mg being given. In those who were benefited, recurrence of the dermatitis was noted within a few days after cortisone was stopped.

One patient who did not benefit from oral cortisone was later given 760 mg of ACTH during a fourteen-day period in the hospital with moderate improvement in his condition. He relapsed to his original state twenty-four hours after ACTH was stopped. Another patient who was not helped by oral cortisone received 820 mg of ACTH during a sixteen-day hospitalization period, with only partial improvement.

Cortisone by injection was given to one patient who was hospitalized with severe atopic eczema. After several days of therapy during which her skin did not improve, this patient developed a severe psychic upset which required discontinuation of cortisone. A second patient treated with 1350 mg of cortisone over a twelve-day period in the hospital was considerably improved but not completely free of dermatitis. Since leaving the hospital she has continued to manifest chronic symptoms similar to those which existed before cortisone treatment.

Urticaria and Angioneurotic Edema.—Two patients with severe serum-sickness type reaction which occurred after penicillin administration were given oral cortisone. Daily doses of 150 to 200 mg resulted in complete disappearance of symptoms within three days. One patient remained well

after the dose was tapered off and discontinued, while the other relapsed four days after the hormone was withdrawn.

Two other patients with chronic urticaria and angioneurotic edema of many months' duration were relieved while taking 100 to 200 mg of cortisone daily in divided doses, but symptoms recurred in one case when the dose was reduced below the level of 100 mg daily, and in the other approximately one week after complete cessation of cortisone.

A fifth patient was hospitalized because of acute urticaria and angioneurotic edema which began following the use of a hair dressing. After failure to respond to antihistamines and other symptomatic drugs during an initial twenty-four-hour period in the hospital, ACTH was given. Following three successive doses, the patient complained of increased pruritis and general discomfort lasting for several hours and thereafter refused further injections of ACTH.

Contact Dermatitis.—Two patients with acute eczematous contact-type dermatitis received oral cortisone. In one patient who was later found to be sensitive to hair lacquer, 50 mg every six hours resulted in remarkable improvement in twenty-four hours, with complete clearing of the dermatitis by the end of the second day. The other case was less spectacularly benefited, but improved greatly during a seven-day period on oral cortisone. In both cases dermatitis recurred within a matter of a few days after cessation of cortisone therapy.

METABOLIC AND HORMONAL EFFECTS

The most frequent metabolic alteration encountered in the use of ACTH and cortisone was the retention of salt and water, despite low sodium intake and supplementary administration of potassium. Increases in weight of 4 to 8 pounds during the course of treatment were noted in ten patients, with the development of edema in six. While some gain in weight could be attributed to improved appetite with consequent added food intake, disappearance of edema and loss of weight usually occurred rapidly after cessation or reduction in dosage. Significant changes in blood sugar, sodium, potassium, or chlorides were not observed, nor were there any appreciable increases in blood pressure noted.

One asthmatic patient who originally manifested a poor clinical and eosinophil response to ACTH, suggesting poor adrenal function, was later given cortisone with a better clinical response. When cortisone was stopped, he developed for several days symptoms suggestive of adrenal insufficiency, although blood chemistry was found to be within normal limits. In a number of instances following the use of oral cortisone, patients have complained of excessive weakness and fatigue.

Hormonal effects such as mild acne and amenorrhea were not uncommon in this series, but in all cases acne disappeared and normal menstrual function resumed after withdrawal of ACTH or cortisone.

Psychic effects such as increased mental stimulation, euphoria, and mild

TABLE VII. THE EFFECT OF INTENSIVE ADMINISTRATION OF ACTH ON BLOOD EOSINOPHIL LEVELS OF HOSPITALIZED PATIENTS

Case	Condition	Total Blood Eosinophils per cub. mm. Blood				Clinical Effect
		Before Treatment	Max. Fall	Day of Max. Fall	Per Cent Change	
1	Asthma	2300	363	6	-84	Good
		621	118	4	-81	Good
		1618	243	5	-85	Good
2	Asthma	272	50	3	-82	Good
		899	67	3	-93	Good
3	Asthma	1133	925	2	-19	Poor
		1600	1040	4	-40	Poor
4	Asthma	436	95	2	-78	Good
5	Asthma	1906	125	4	-94	Poor
6	Asthma	1585	305	4	-81	Fair
7	Asthma	1176	66	4	-94	Good
8	Asthma	598	45	3	-92	Good
9	Asthma	1143	111	3	-90	Good
10	Asthma	127	33	3	-74	Fair
11	Hay fever	400	88	4	-78	Good
12	Hay fever	955	200	3	-80	Good
13	Hay fever	1176	77	3	-94	Good
14	Eczema	431	175	6	-60	Fair
15	Eczema	339	73	5	-79	Fair
16	Urticaria	881	75	2	-92	Poor

depression were frequently noted. In two cases striking effects occurred. One patient developed frankly psychotic behavior during cortisone administration which persisted after therapy had ceased and required transfer to a mental hospital where shock treatment was given, with eventual improvement. A second patient developed marked mental depression and paranoid behavior during the first week of ACTH treatment but improved after the course was completed.

EOSINOPHILS

A fall in the level of blood eosinophils is considered to be relatively a sensitive gauge of increased cortical function.[13] Under the influence of ACTH or cortisone there occurs a very marked depression of such cells in the majority of patients which in our experience does not necessarily bear a constant relationship to the clinical effects induced. Some whose symptoms are poorly influenced show a very marked eosinophil depression, while an occasional patient who is greatly helped manifests a very slight fall in these cells.

In the present study, total blood eosinophils were determined before treatment and at daily intervals afterwards in hospitalized patients, and at least twice weekly in ambulatory cases. The maximum fall in eosinophils in those receiving ACTH (Table VII) every six hours occurred between the second and sixth day. All patients who were completely relieved of symptoms showed a reduction of 78 per cent or greater. In those who were moderately helped or not at all benefited, the fall in eosinophils was from 74 to 94 per cent in all but two cases. The maximum depression occurring in one patient who made no improvement on ACTH was 19 per cent. Treatment with cortisone in this patient, given

TABLE VIII. THE EFFECT OF INTENSIVE ADMINISTRATIONS OF PARENTERAL CORTISONE ON BLOOD EOSINOPHIL LEVELS OF HOSPITALIZED PATIENTS

Case	Condition	Total Blood Eosinopnils per cub. mm. Blood				Clinical Effect
		Before Treatment	Max. Fall	Day of Max. Fall	Per Cent Change	
1	Asthma	762	156	4	−80	Good
2	Asthma	588	128	5	−78	Good
3	Asthma	1133	Increase	—	—	Fair
4	Asthma	800	50	6	−94	Good
5	Asthma	1399	33	10	−98	Poor
6	Asthma	1230	10	11	−99	Fair
17	Asthma	1580	96	4	−94	Poor
18	Asthma	862	93	3	−89	Good
19	Asthma	175	55	3	−69	Fair
20	Asthma	610	216	4	−65	Fair
21	Asthma	1140	622	55	−46	Poor
22	Eczema	865	5	3	−94	Poor
23	Eczema	788	111	6	−86	Fair

immediately afterwards, failed to depress the eosinophils below the starting levels, although some clinical improvement did occur. A second course of ACTH during a period when the patient manifested clinical symptoms of adrenal insufficiency, caused a reduction in eosinophils of only 40 per cent, without improvement in the asthmatic state. The second case was a patient with atopic eczema who was only moderately improved during ACTH therapy and showed a reduction of 60 per cent in blood eosinophils.

Patients under treatment with cortisone suspension while in the hospital showed a maximum depression in the level of blood eosinophils between the third and eleventh day (Table VIII). A fall of 78 to 94 per cent was recorded in four patients who were completely relieved of symptoms during therapy. In four patients who were moderately improved, a fall of 65, 69, and 99 per cent occurred in three, while the fourth patient showed an increase over starting levels. The eosinophil depression in three cases who were not helped ranged from 46 to 98 per cent.

Ambulatory patients under treatment with orally administered cortisone showed a maximum fall in eosinophils between the second and fifth day of treatment. In those who attained the maximum improvement from such treatment, the fall ranged from 70 to 98 per cent in all but one case. In this patient, whose asthma was completely relieved after forty-eight hours of treatment, the maximum depression in blood eosinophils was not over 10 per cent. All but two patients who did not respond to treatment or who were only partially improved showed a fall of 74 to 96 per cent. In one of these a drop of 32 per cent occurred, while parenteral administration of cortisone later caused a depression of 94 per cent over pretreatment levels. This greater change in eosinophils, however, was not associated with any increased clinical response. A second patient who failed to show any depression in eosinophils during oral cortisone treatment was later benefited by injectable cortisone and at the same time showed a 78 per cent reduction in these cells.

DISCUSSION

Since symptoms in chronic disease states tend to recur shortly after withdrawal of ACTH or cortisone, various methods of administration have been considered in efforts to prolong the period of freedom induced by these hormones. Repeated short courses; an intensive course followed by a daily or intermittent maintenance dose; alternate courses of each hormone, and the combined use of both hormones have been suggested.[4] Our own attempts to prolong the remissions in allergic diseases have been far from satisfactory. After an intensive course of ACTH or cortisone by injection the remission periods have been but briefly extended by giving the hormones in smaller amounts two or three times weekly, or even daily. In the case of orally administered cortisone, determination of a daily maintenance dose is exceedingly difficult. An amount which appears capable of keeping the patient in full or partial remission may after a week or two become insufficient, and it again becomes necessary to increase the dose in order to control symptoms. Any plan of prolonged administration must of course take into consideration the increased possibility of metabolic and hormonal effects as well as changes in the structure and function of the adrenal cortices. Alternating or combined administration of cortisone and ACTH have been suggested to counterbalance the adrenal atrophy resulting from the use of the former against the adrenal hyperplasia induced by the latter.[4]

Since one is dealing with the hypersensitive state in which it is presumed that an antigen-antibody mechanism is involved, it is important to know the effects of increased adrenal cortical function on the immune responses of the body. Many studies have attempted to elucidate these problems, some of which are at considerable variance with each other. Antibody titers in some instances are reported to be elevated,[2] depressed in others,[7] while still other controlled studies have shown no interference in the appearance time or quantity of antibody.[9] In our own experiments ACTH did not alter the normal susceptibility of intact guinea pigs to histamine or to anaphylactic shock.[4] The Arthus reaction, passively induced, is not prevented by treatment with cortisone,[3] but inhibition in the development of the active Arthus phenomenon has been reported to occur, associated with a failure to develop antibody.[7] Immediate whealing skin responses to histamine or specific antigen and passive transfer sensitization in human skin are not affected, nor is the reagin titer of the blood of allergic patients significantly changed. In some instances tuberculin reactions and delayed bacterial skin responses are reduced or obliterated. In a recent study carried out in our own laboratory, the eczematous response to a challenge dose of paraphenylenediamine or 2-4 dinitrochlorobenzene in sensitized guinea pigs was not prevented by cortisone.[5]

Another extremely important phase of pituitary-adrenal cortical function related to immune responses is recent observations that ACTH and

cortisone may have a deleterious effect on the course of bacterial infection. Rabbits receiving large daily doses of cortisone prior to and during the course of intradermal injections with Group A hemolytic streptococci developed septicemia and death in every instance, while control animals survived the same doses of streptococci without the development of demonstrable bacteremia.[11] In experimental streptococcal and pneumococcal infections in mice, those receiving ACTH and cortisone were unable to handle infections as well as controls.[8] Our own clinical observations indicate that patients under treatment with ACTH and cortisone are more susceptible to intercurrent infection, and flareups of previously latent infections are not uncommon. Adequate antibiotic therapy is essential to control the infectious complications of the disease under treatment.

From the experiences gained in the present study together with those of other investigators, it can be anticipated that stimulation of the adrenal cortex by ACTH or the administration of cortisone will frequently alleviate severe symptoms associated with the hypersensitive state. The changes which take place under the influence of increased adrenal cortical function are of a temporary nature, and there appears to be no alteration of the underlying disease process. The exact nature of these changes and the relationship to the immune response of the body is poorly understood and requires considerable clarification before the place of such agents in the long-term management of diseases of hypersensitivity is established. Where symptoms are self-limited or of short duration, as in the case of seasonal hay fever, intensive administration of ACTH for a period early in the season, or the continued administration of adequate doses of cortisone during the pollinating period may be worthy of consideration as possible therapeutic methods. In chronic states, the principal advantage derived, at least on the basis of present experience, is in the alleviation of severe distress for a sufficient period of time to break the vicious circle of symptoms frequently encountered in allergic-type reactions. While remissions are of relatively brief duration, the symptoms which recur may perhaps be more readily controlled in some instances by more conventional therapy. It has been our experience, however, in at least three cases in the present study, that the symptoms recurring after successive courses of ACTH or cortisone have been of greater severity than those which existed prior to the initiation of such treatment. Whether this has occurred because of, or in spite of, hormone treatment cannot be determined from present evidence. At the present time, ACTH and cortisone must be considered as therapeutic adjuvants which may be of advantage when used for short periods of time in severe allergic disease. The indications for such use appear to be extreme distress which does not readily respond to conventional symptomatic measures. Whether these agents render any real service to the patient beyond their immediate effects, or whether they may in fact be detrimental to the individual as far as the eventual control of the chronic state is concerned, remains to be determined.

SUMMARY

1. ACTH and parenteral and oral cortisone were frequently effective in promptly relieving severe bronchial asthma, hay fever, urticaria, and atopic and contact eczema. Not all cases responded favorably.

2. The effects of ACTH and oral cortisone were more quickly evident than were those of parenterally administered cortisone suspension. The effects of orally administered cortisone appeared to be dissipated most rapidly.

3. In chronic states such as bronchial asthma, the remissions induced by courses of ACTH and cortisone were generally of brief duration, with symptoms recurring in their original severity within a matter of days or weeks. While the response to repeated courses was frequently as good as to the original, there was a tendency for symptoms to recur more quickly and severely after successive courses had been given.

4. In seasonal hay fever, intensive administration of ACTH at six-hour intervals, large single daily injections of cortisone suspension, and four-hourly administration of cortisone orally were effective in relieving symptoms.

5. Hormonal and metabolic side effects encountered during this study were fluid retention with edema, acne, menstrual dysfunction, adrenal insufficiency, and psychic disturbances.

6. Present evidence indicates that ACTH and cortisone may be used to advantage as adjuncts in the temporary alleviation of severe symptoms associated with the hypersensitive state. The advisability of using them for long periods of time in such conditions is questionable.

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(Continued on Page 652)

ADRENOCORTICOTROPIC HORMONE (ACTH)
Effect on Ragweed Hay Fever

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THE antiragweed hay fever effects of adrenocorticotropic hormone (ACTH) were first reported by Randolph and Rollins.[1,2] After the second day of ACTH therapy there was virtually complete relief of symptoms, which in three of their four cases persisted throughout the remainder of the season. The fourth patient had a recurrence of mild hay fever on the fourth day after the treatment was stopped. In some cases the hyposensitization and drug therapy of ragweed hay fever and its complications still leave much to be desired. For this reason it was considered justifiable to study further the effects of ACTH in this disease, with particular reference to office treatment in intractable severe hay fever, with or without bronchial asthma.

Eight patients with ragweed hay fever complicated by seasonal bronchial asthma were selected for study. It is of special interest that the ragweed pollen counts in Chicago for 1950 were the lowest ever recorded. Despite this, the severity of hay fever and asthma in the cases to be reported was as great as in previous years according to the patient's own report and my direct observation. Symptoms were evaluated on the basis of daily personal observation and a daily record of symptoms made by the patient every three hours on a scale of 1 to 4 plus, 1 plus indicating minimal and 4 plus maximal symptoms. The blood pressure, weight, and findings of urinalysis were recorded daily, and blood sugar determinations were made once a week. The only modification of the diet was the restriction of sodium chloride to two grams daily. Supplementary therapy consisted of an antihistaminic drug for the relief of severe hay fever, and ephedrine with or without aminophylline for the relief of severe bronchial asthma. Each patient was instructed to measure and administer ACTH just as the diabetic is taught to give insulin. Patients were further told to keep a daily weight chart and to make daily urine analyses for sugar.

REPORT OF CASES

Case 1.—A white woman, aged forty years, had had ragweed hay fever, ragweed bronchial asthma, and perennial vasomotor rhinitis for the past fifteen years. On September 1 and 2, 1949, she was treated with intramuscular ACTH, 25 mg every six hours. This was followed by complete relief of the asthma and hay fever for the remainder of the season. On August 28, 1950, when ACTH was started, her asthma and hay fever were 4 plus. For two days 25 mg of ACTH was given every six hours, the dosage then being reduced to 12.5 mg every six hours. On August 30 the asthma was relieved entirely, but hay fever persisted with moderate severity.

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From September 1 to September 5, 12.5 mg of ACTH was continued every eight hours, with relief of the asthma. The hay fever continued in moderate severity through September 25, when it terminated.

Case 2.—A man, aged thirty years, had had hay fever in August and September for sixteen years accompanied by bronchial asthma throughout the season the past fourteen years. On August 24, 1950, he presented 4 plus hay fever and one plus asthma. He was given 25 mg of ACTH every six hours but did not note any relief of symptoms until August 27, when he became free from asthma and the hay fever was reduced in severity to 1 plus. At this time he noted a decided "peppy feeling" and increased appetite, but suffered from heartburn. The heartburn was relieved by aluminum gel. On August 29, when he had few or no symptoms, the dosage of ACTH was reduced to 12.5 mg three times a day, and on September 1, to 12.5 mg twice a day. On September 8 the symptoms of hay fever and asthma increased to 2 plus. Then 12.5 mg of ACTH was given every six hours, with reduction of the symptoms to 1 plus. From September 12 to September 21 the ACTH injections were reduced to 12 mg twice a day, then discontinued entirely. Hay fever recurred for several days but disappeared entirely by the end of September. When the therapy was stopped, the patient noted a "let-down" feeling which persisted for eight days.

Case 3.—A white man, aged twenty-seven years, was hospitalized July 5, 1950, for treatment of generalized atopic eczema. The eczema started at the age of two years and cleared up at the age of three years, when he developed hay fever in August and September, accompanied by bronchial asthma, both of which persist to the present time. Flexural eczema recurred at the age of eleven years and has gradually increased in extent and severity. ACTH in 20 mg doses every six hours was given from July 7 to July 15, with complete relief of skin itching and sharp decrease of lichenification. The patient was discharged from the hospital July 17, taking 12.5 mg of ACTH three times a day; his dose was gradually reduced to 10 mg twice a day until August 21, when 4 plus symptoms of hay fever and asthma developed. The skin maintained its original improvement. ACTH was increased to 10 mg four times a day, but the hay fever and asthma persisted between 1 and 2 plus; on August 29, 15 mg of ACTH was given three times a day until September 7, when 4 plus hay fever and asthma developed. This was reduced to 1 plus and 2 plus levels with an increase of the dosage to 15 mg four times a day until September 16, when the dose was reduced to 12.5 mg three times a day. This dose was gradually reduced to 12.5 mg daily until October 10, when it was discontinued even though 1 plus asthma persisted.

Case 4.—A white woman, aged twenty-three years, married, was first seen August 21, 1950, for ragweed hay fever of eight years' duration, accompanied in the past four years by bronchial asthma. There was some cough and nasal congestion all year, and when the patient was in Texas she had severe asthma and hay fever during November and December. Under conventional therapy she progressed satisfactorily until September 7, when the cough and hay fever abruptly became intractable. ACTH given in 12.5 mg doses intramuscularly four times a day caused detectable relief within four hours. Relief was progressively and increasingly rapid until September 10, when 1 plus symptoms remained. On September 16 there was a sudden exacerbation of all symptoms coinciding with the increase of symptoms noted in other patients. The pollen count on this date was only 8 per cubic yard, but large amounts of dust were observed on the twenty-four hour slides. On September 17, 12.5 mg of ACTH was given twice daily, and on September 28 reduced to once daily. On October 4 the therapy was discontinued because, except for a slight cough, the patient was symptom-free.

Case 5.—A white woman, aged fifty-two years, had had hay fever and asthma in August and September for ten years with some nasal congestion and sneezing all year. She presented the findings of 4 plus hay fever and 2 plus asthma on August 26, when she was placed on 20 mg of ACTH four times a day. The hay fever improved to a 3 plus level in two days and a 2 plus level in six days, but did not decrease below this point. On September 5 the dosage was gradually reduced, and on September 9 discontinued entirely. The patient stated that the relief was not nearly so satisfactory as that obtained with conventional therapy the previous five years.

Case 6.—A white woman, aged twenty-six years, had had hay fever and bronchial asthma in August and September for four years. She was seen on August 28 with 4 plus hay fever and 1 plus asthma, for which 25 mg of ACTH was given four times a day. This reduced the hay fever to a 2 plus level in two days. The dosage was then decreased to 12.5 mg three times a day until September 4, when it was discontinued even though 2 plus symptoms persisted. On September 5 and 6, with pollen counts of 57 and 65, respectively, the asthma increased to four plus and the hay fever to three plus. On September 7, 12.5 mg of ACTH was started four times a day. On September 12 the hay fever was 1 plus and there was no asthma. The medication was gradually reduced, and on September 18, when the patient was symptom free, it was stopped. The ingestion of red and green peppers, which produced hay fever and asthma at any time of the year, resulted in a like effect despite ACTH therapy.

Case 7.—A white woman, aged fifty years, had had hay fever in August and September for thirty-six years and complicating bronchial asthma for twenty years. Hay fever started August 20, 1950, and on August 22, 25 mg of ACTH was started four times a day. Four plus hay fever persisted for twenty-four hours, but at the end of that time relief began and became complete on August 25. The ACTH was then discontinued. On August 28, 2 plus hay fever recurred and 25 mg of ACTH was given twice daily to September 2, when the symptoms increased to 4 plus hay fever, and 25 mg of ACTH was given four times a day to September 6. On this date there was no hay fever and the therapy was discontinued. On September 16 acute 3 plus hay fever developed with a pollen count of 8 per cubic yard. This continued up to September 20 and recurred during the period from September 25 to September 29.

Case 8.—A white man, aged forty-six, had been subject to severe ragweed hay fever for the past twenty years, and to bronchial asthma accompanied by hay fever for ten years. He received ragweed therapy in 1945 without apparent benefit. Beer and bourbon whiskey resulted in wheezing, particularly during the pollen season. Hay fever and asthma started on August 19, 1950, developing to 4 plus severity by August 25, when 25 mg of ACTH every six hours was started. There was sharp improvement of symptoms in twelve hours, with complete relief in thirty-six hours. After treatment with ACTH for three days this therapy was discontinued on August 28. On September 2, five days later, the asthma and hay fever recurred; repeated treatment with ACTH was followed by relief of symptoms as before. Eosinophils were absent prior to therapy and remained absent.

DISCUSSION

Eight patients with ragweed hay fever and bronchial asthma were treated with ACTH, with variable results depending somewhat on the initial and maintenance dosage of the drug. One patient obtained almost complete

relief from 12.5 mg of ACTH four times a day as an initial dose, and one, from 15 mg four times a day. Of the remainder, who were given 25 mg four times a day as starting doses, all except one, who was completely relieved of hay fever, continued to have hay fever of from 1 to 2 plus severity. It would appear that an average starting dose of 25 mg four times a day is not excessive and that an average maintenance dose of 15 mg is necessary for the adequate relief of hay fever.

In general, the asthma was relieved sooner and more completely than the hay fever. In nonseasonal asthma not related to pollen, ACTH has been reported and observed by us to give relief for periods as long as four months. On the other hand, asthma and hay fever due to ragweed pollen recur within three to five days during the pollen season after the discontinuance of ACTH therapy. In one of the cases hay fever recurred the first day after the ACTH was stopped. While receiving ACTH, one patient tolerated known food allergens without symptoms and one did not.

There were no immediate undesirable side effects detected except in one patient who had a "let-down" feeling for several days after the ACTH was discontinued. Abrupt cessation of therapy did not appear to produce side effects. Four months after discontinuance of the ACTH therapy in the dosage employed there are no evidences of remote side effects.

In the cases reported by Randolph and Rollins,[1] blood eosinophils dropped to zero levels before the therapy was discontinued. Skin biopsies of ragweed wheals on the same patients reported by Zeller, Randolph and Rollins[2] revealed few or no tissue eosinophils after ACTH treatment. In the cases reported here, in which similar initial doses were given and the treatment was continued for a much longer period, the eosinolytic effect of ACTH was not nearly so great, nor was the therapeutic effect as complete or as sustained. The reason for this is not known. It may be that, even though the pollen count was the lowest ever recorded for the Chicago area, there were other unknown inhalant or ingestant factors which created and increased the total allergic load on this group of subjects. Perhaps, as suggested by Randolph,[1] larger doses of ACTH to produce complete eosinopenia may be a guide to the dosage required for prolonged and complete relief. It is my impression that severe ragweed hay fever with or without bronchial asthma which fails to respond to conventional therapy can be justifiably and adequately managed by the administration of ACTH as an office procedure in the same manner that the diabetic is taught to give his own insulin and provide daily urine analyses and weight records.

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THE ABSORPTION OF ONE PER CENT CHLORCYCLIZINE HYDROCHLORIDE CREAM* THROUGH THE SKIN

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THE ORAL administration of chlorcyclizine hydrochloride has been found to be very effective in relieving many allergic conditions.[2,4,5,6,8,9] Only minimal undesired side effects have been observed.[3,7] Topical application on localized areas of allergic reactions in several hundred patients has likewise been proven to be useful, with not one instance of sensitization even in cases requiring long periods of treatment.[1] Since topical application of the antihistamine is of proven value, the estimation of the amount of chlorcyclizine hydrochloride that can be absorbed through the skin should be of especial interest. This has been studied by biologically assaying the amount of the substance in the blood plasma of dogs in the following manner after inunction of 1 per cent chlorcyclizine hydrochloride cream on areas of intact skin.

The hair on the backs of dogs was closely clipped with an electric shaver, and a 1 per cent chlorcyclizine hydrochloride cream was vigorously rubbed on the skin of each animal twice a day, five days per week, for a period of one month. Excess cream was removed with a paper towel. It was calculated that an area of 400 sq cm of skin was inuncted, corresponding to approximately 12 per cent of the total surface area of each animal. It was also estimated that 30 mg of chlorcyclizine hydrochloride was retained by each dog daily. The animals were never observed to lick the inuncted areas. A control test was made by using a placebo ointment, i.e., the ointment base without the antihistaminic drug. Skin sections were taken at the end of the inunction period for histological examination. The dogs were shaved at least once per week during the test period.

The amount of the antihistamine in the blood plasma of each animal was evaluated at weekly intervals during the test by determining any inhibitory action of the plasma on histamine-induced contractions of guinea pig ileum using the Magnus technique. From .1 γ to .2 γ/ml of histamine diphosphate was found to produce convenient submaximal contractions. Five ml samples of blood were taken during the middle of each weekly inunction period by means of a 10 ml syringe containing .2 ml of heparin solution, 1 mg per ml physiological saline. Clear plasma was obtained by centrifuging for twenty minutes at 15,000 rpm. Syringes and centrifuge tubes were all coated with silicone to prevent hemolysis of the blood. The isolated strips of guinea pig ileum taken from the gut immediately above the cecum were suspended in 10 ml constant temperature baths

From the Wellcome Research Laboratories.
* Supplied as 'Perazil' brand Chlorcyclizine Hydrochloride Cream by Burroughs Wellcome & Co. (U.S.A.) Inc.
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TABLE I. PLASMA LEVELS OF CHLORCYCLIZINE HYDROCHLORIDE IN INUNCTED DOGS
Y per ml Plasma

Dog	Wt.	Days during Inunction Period					
		0	3	10	17	24	30
T	6.6 kg	0	.67	.13	.17	<.04	<.04
B1-1	8.9 kg	0	.26	.10	.23	.18	.13
B1-2	7.5 kg	0	.09	.27	.25	<.04	.06

TABLE II. PLASMA LEVELS OF CHLORCYCLIZINE HYDROCHLORIDE AFTER INTRAMUSCULAR INJECTIONS
Y per ml Plasma

Dog	Dose	0	½ hr.	4½ hrs.	2 days	3 days	13 days
T	10 mg/kg wt.	0	.63	.37	.38	.08	0
B1-1	5 mg/kg wt.	0	.34	—	.23	—	—

(37.5° C) containing Tyrodes solution aerated with oxygen. The section of gut was secured at either end by wire clamps** situated on the same side of the tissue cylinder so that a half-inch longitudinal muscle section would be the active material. The actual amount of inhibition was determined from a log dose response curve obtained by adding different amounts of chlorcyclizine hydrochloride to blood plasma containing no inhibitor. It is interesting to note that the same amount of chlorcyclizine hydrochloride in saline solution would give twice the inhibition value as that obtained when plasma was present, possibly indicating some union or action with the plasma protein that does not permit it to become active against histamine. Usually .1 to .5 ml of plasma from the treated dogs was used in such determinations. At no time did the plasma from untreated animals give inhibitory responses.

Results of typical experiments are included in Table I. From these data it will be seen that small but appreciable amounts of the chlorcyclizine hydrochloride do penetrate the skin and may be determined in the blood stream. Traces of the antihistamine could be found in the plasma for over a week after the inunction had been discontinued.

Similar determinations were made in two of the above dogs after intramuscular injections of different dosages of the antihistaminic drug. This was done in order to determine what amounts would be required to produce blood plasma levels of the same magnitude as those obtained after inunction. Results are given in Table II.

It appears that the plasma level of the drug remains rather low after administration whether by inunction or by intramuscular injection.

In order to determine the plasma level of the chlorycyclizine hydrochloride at which definite toxic symptoms could be observed, extremely high doses (25 mg per kg body weight) were given orally to the animals

** Tissue Clamps No. 50-271, Phipps & Bird, Inc.

daily by capsule twenty minutes after the regular morning feeding. No toxic symptoms were observed after the first dose, but on the second day some two to three hours after that day's dosing, the dogs became apprehensive, with nervous tremors and twitching of the head, neck and limbs. Samples of the blood were taken at this time, and it was found that the plasma levels of the antihistaminic drug had risen appreciably. These values are given in Table III.

TABLE III. PLASMA LEVELS OF CHLORCYCLIZINE HYDROCHLORIDE *Y* PER ML AFTER ORAL ADMINISTRATION
25 mg per kg Body Wt per Day

Dog	Days of Dosing		
	0	1*	2**
T	0	—	4.08
B1-1	0	—	5.40
B1-2	0	—	3.88

*No symptoms were observed; therefore no samples were taken.
**All dogs exhibited symptoms of apprehensiveness, with nervous tremors and twitching of the head, neck and limbs.

These results indicate that while a single high dose of 25 mg per kg body weight was not in itself obviously toxic, subsequent doses build up so that toxic symptoms do appear even after the second dose. The plasma level at which these symptoms occur was about twenty times that of the inuncted dogs.

TABLE IV

Drug	No. of Rats	Average Starting Wt	Average Wt at End of 28 days	Average Gain	Food Consumption Total for 1 Rat for 28 days
1% Chlorcyclizine Hydrochloride Cream	10	54.2 Gm	142.1 Gm	87.9 Gm	337 Gm
Placebo Cream	10	53.9 Gm	141.5 Gm	87.6 Gm	315 Gm
Controls	10	50.1 Gm	143.8 Gm	93.7 Gm	333 Gm

The possible toxicity arising from topical application has also been studied in rats. Ten growing rats (Carworth Farms), weighing 45 to 60 Gm each, were placed in cages (five to a cage), and given a ground fox chow diet and water *ad libitum*. Each week the fur on the backs was removed with an electric razor. The 1 per cent chlorcyclizine hydrochloride cream was rubbed into the skin twice per day for twenty-eight days. Two other groups were considered the controls: one was shaved and rubbed with a placebo ointment and the other had no treatment. An average of .13 Gm of the cream was rubbed on an area of 35 sq cm, or about 1.3 mg of the drug would be left in and on the skin of each animal twice a day. The growth rates and food consumption are presented in Table IV.

No significant difference could be determined between the growth rates and food consumption of any of the three groups, thus supporting the conclusion that the antihistaminic cream had no ill effects on these criteria of well being.

Autopsies and histological examinations, especially of the skin, likewise gave no indication of any toxicity in the rats or dogs being treated with the 1 per cent chlorcyclizine hydrochloride cream.

SUMMARY

A study has been made of the topical application of 1 per cent chlorcyclizine hydrochloride cream. It was found that a very small amount of the drug was absorbed through the intact skin of dogs. The antihistaminic agent could be detected in the blood plasma by means of a sensitive biological method. The amounts determined were only about one-twentieth of those associated with the appearance of toxic symptoms.

The growth rates and food consumption of growing albino rats treated daily with the cream were not significantly different from those of controls during a test period of twenty-eight days.

No pathological symptoms, either gross or histological, were observed in any of the animals inuncted with the 1 per cent chlorcyclizine hydrochloride cream.

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CEL-O-SEAL BANDS

Cel-O-Seal Bands for sealing allergy extract vials, as mentioned on page 501 of the July-August issue of ANNALS OF ALLERGY in a communication from S. William Simon, M.D., of Dayton, Ohio, are now stocked by Allergists Supply Co., 458 Broadway, New York 13, N. Y. These are available at practically cost to regular customers. The size of the opaque white Cel-O-Seal bands is 19 mm x 23 mm.

THE TREATMENT OF ALLERGIC HEADACHE

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THREE of the most common complaints of mankind are constipation, colds, and headaches. This statement can be verified by druggists as well as by physicians. In a recent statistical study,[2] I surveyed the incidence of headache in 4,634 individuals in New Orleans. This survey was made possible by a grant from Sandoz Pharmaceuticals to the Louisiana State University School of Medicine. A standard questionnaire was used, and the material was divided into four groups so that the data could be cross-checked. The information on the questionnaires was transposed to IBM cards, from which statistical computations and analyses were made. Realizing that figures of this type might be open to controversy, a statistician (Dr. Huldah Bancroft, Professor of Biostatistics, Tulane University School of Medicine) tested some of the results for the probability of error. While the exact data will be found elsewhere,[2] some of the findings were as follows:

The incidence of all types of headache in the general population is 64.8 per cent. Among those with headache there is a significantly higher proportion of individuals with nasal and also chest and throat complaints. There is also a much higher incidence of "colds" among headache sufferers. It is probably true that many disorders of the respiratory tract are undoubtedly allergic in nature, even though not demonstrably due to sensitization to extraneous antigens. The same trend was seen in individuals with hives and allergic skin diseases, although the statistical base here was not high enough to be significant. Another significant finding was the fact that there is a higher incidence of a familial history of allergy among persons with headaches. These data indicate mathematically and statistically the relationship between headache and clinical allergy.

In other data (as yet unpublished),[3] the incidence of migraine was found to be relatively low among all types of headache. It was also found that the frontal type of headache greatly predominates, and was reported in 72.6 per cent of all types of headache. Histaminic cephalalgia (Horton's syndrome) is extremely rare.

In the first study,[2] it was also found that headaches are more common among females, younger adults (headaches tend to decrease with advancing age), and single people—who reported more headaches than married ones. Also, people with higher education reported more headaches than those with little or no education. In addition, occupations which embody

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more mental stress and exertion, such as executives, students, and professional groups, have more headaches than other occupations, such as manual laborers. The statistical data above described also indicate that there often is an allergic basis for the complaint of headache. It is difficult to avoid the conclusion that the lability of the cranial vessels is affected by a number of factors: endocrine disturbances, age, mental and emotional problems, various allergic states, et cetera.

Headaches have been classified in many ways: extracranial and intracranial, vascular and nonvascular, psychogenic and nonpsychogenic, migrainous and nonmigrainous, nasal and nonnasal, histamine-produced and nonhistamine-produced, et cetera. It is thought that most headaches are vascular in type and are due to dilation of the extracranial or intracranial arteries, with an increased amplitude of pulsation of the vessels.

Cranial vasoconstrictor drugs, such as the ergotamines, have long been used in the treatment of vascular headache. The response of the migrainous patient to the ergotamines has been regarded as a diagnostic point.

It was shown that the most common type of headache is the frontal variety. In another study,[1] I will show that there is a connection between nasal symptoms and frontal headache. Therefore, the response of the patient with simple frontal headache to the ergotamine drugs was a question which required still further amplification. A number of office patients with a major complaint of frontal headache were selected, and their response to the ergotamines for symptomatic relief was evaluated. In a series of eighteen individuals, fifteen reported good results after the administration of dihydroergotamine (DHE 45). Three patients reported partial relief. Also in nineteen patients with frontal headache, sixteen reported good results after the use of Cafergot. One had partial results, another had questionable benefit, while one patient received no relief. The required amount of Cafergot was usually small, only two individuals requiring more than three tablets for an attack. Four patients were used in both groups.

It may, therefore be concluded that the ergotamine drugs give symptomatic relief in an impressive percentage of all cases of frontal headache. While some investigators may ascribe this relief to other factors, such as nasal decongestion, the author feels that the relief is due to the constricting effect of the ergotamine drugs on vessels such as the anterior meningeal branches of the ophthalmic arteries. In this other study,[1] it is pointed out that the anterior and posterior ethmoid vessels, which supply the nose, are also branches of the ophthalmics, before they give off the anterior meningeal branches. It is felt that nasal obstruction or edema acts as a trigger mechanism which may initiate dilation of the anterior meningeal vessels.

Also in this frontal type of headache, other manifestations which indicate the vascular basis are often seen. These include prodromal symptoms such as aurae, visual changes, nausea and even vomiting, throbbing type of headache, et cetera.

Many otorhinolaryngologists no longer feel that frontal headache is due to a vacuum in the frontal sinuses, which was thought to follow obstruction of the nasofrontal ducts.

In order to obtain the best results, the ergotamine drugs must be properly administered. DHE 45 is used in dosage from 1 to 2 or even 3 cc. It is given 1 cc every half hour until relief is obtained or until 3 cc are taken. It is recommended that no more than 3 cc be taken in a week. Sometimes less than 1 cc gives relief. This indicates that there is a great variation in the amount required for different individuals. The dosage really should be tailor-made.

Cafergot (formerly Cafergone or EC 110) consists of 100 mg caffeine and 1 mg of ergotamine tartrate. These two drugs have a synergistic effect. Failures reported after the use of Cafergot are often due to the fact that the physician has given improper directions to the patient. I have actually seen prescriptions calling for one Cafergot tablet t.i.d. It should be used as early as possible in order to obtain the best results. It may abort an impending attack, even though the prodromal manifestations are associated with vasoconstriction, and actual head pain may not as yet have begun. If it is to be used at all it must be used in sufficient quantity to obtain the pharmacologic response. The blood level of the drug determines its pharmacologic effect within the individual, and it varies from one individual to the next. One tablet t.i.d. is not likely to prevent headaches.

After a headache has become well established, it is thought that symptoms may be perpetuated by edema of the vessel wall. Not even ergotamines can help the patients in this phase except in rare instances. Here the treatment is time and sedation. I refuse to give patients ergotamine treatment for the latter part of a headache, because since relief is not likely, the patient would be mentally conditioned against the use of it in future attacks.

Cafergot is given in the following way. The dosage again will vary according to the patient, the timing, and the severity of the attack. Two tablets are usually taken at the onset of symptoms. Often one is enough. If there is no relief after a half hour, another tablet is taken. This may be repeated every half hour, up to six tablets, or until relief is obtained. When the interval between additional tablets is too long, the factors of drug elimination and progressive edema of the vessel walls hinder the full pharmacologic effect. No more than ten tablets are taken in a week. The patient soon determines exactly the amount that he requires and is then able to take the full dose at the first onset of symptoms. As stated above, the amount required may vary in the same individual, dependent on the intensity of pain.

When ergotamine drugs are used it is best to keep the patient quiet after their administration. If activity, work, or excitement continues, there may be greater likelihood of a side reaction. This reaction often

consists only of mild nausea. Or it may become more severe and even vomiting may result. Paresthesias, numbness, muscular pain, and abdominal pain may follow. If gastric symptoms are prominent, a belladonna preparation may be tried.

Hyperergic, or exaggerated normal reactions may occur to drugs. With Cafergot, this could be an exaggerated reaction to the caffeine component. This could cause insomnia, "nervousness," and mental upset. For this type of individual DHE 45 is suggested. Or, if preferred, Cafergot could be given in conjunction with a barbiturate.

Contraindications for all of the ergotamines are peripheral vascular disease, angina pectoris, organic heart disease, hypertension, impaired renal or hepatic function, and septic states associated with intravascular foci. DHE 45 is nonuterotonic, but ergotamine tartrate and Cafergot are uterotonic, and hence these latter two preparations should be avoided during pregnancy.

In these studies, I have been particularly interested in results obtained with the ergotamines in frontal headache, and also with the more specific management which will be discussed later. Other symptomatic medications are better described elsewhere.

Another drug that is being used in the treatment of headache is an antispasmodic, Octin, and some favorable reports have appeared in the literature. My experience with it has been too small to enable me to draw any concrete conclusions. This drug may be indicated in some patients, where the ergotamines are contraindicated. It may have a hypertensive effect, and a test dose using a small quantity should be given.

Several years ago it was claimed that a vasodilator, nicotinic acid, could be used during the stage of vasoconstriction. The limited extent of its use indicates that it must be inconsistent or unreliable.

The inhalation of oxygen has been recommended by some, but the results are again apparently variable.

Mild analgesics are quite popular and are preferred by 81 per cent of headache sufferers.[2] A preparation such as aspirin may relieve a mild headache but not a severe one. It was found that 82 per cent of all cases of all types of headaches are not being treated specifically for this complaint by any kind of physician.[2] Therefore, it must be remembered that most headaches are mild, self-diagnosed, and self-treated. The ergotamine drugs and the narcotics are available only on prescriptions. Narcotic drugs are not permissible because of the grave danger of addiction. Many headaches tend to recur at frequent intervals. Furthermore, aspirin merely masks the pain by raising the threshold, whereas the ergotamine group alters the source of pain. Hence the expression, "I get a little relief with aspirin—but the pain always returns."

I have observed that antihistaminic drugs give help in many instances. It is probable that many of these cases are definitely associated with nasal allergy.

A fair percentage of patients report relief after the use of nose drops,[2]

especially when used in the lateral head low position. Here again, in this group, we may see that nasal allergy and nasal symptoms are associated with the development of the headache. A vasoconstrictor nose drop obviously lessens nasal mucosal edema. If the mechanism of frontal headache is as described above, pressure might then be removed from the ethmoid vessels.

Some otorhinolaryngologists feel that they can relieve frontal pain by cocainization of the septal branch of the nasociliary nerve. I have had no experience with this procedure. I also have had no experience with the use of intravenous histamine in the treatment of headache.

If nasal symptoms are associated with headache, it is obvious that many of these cases are primarily due to nasal allergy. Therefore, attention must be directed to a correct etiological diagnosis. Usual skin testing procedures are employed, with especial emphasis on inhalant allergy. The major cause of perennial symptoms in my experience has been sensitization to house dust,[4] but other inhalant antigens or pollen may be responsible. Hyposensitization may give complete relief, or we may see only a lessening of the severity and frequency of attacks. I have also found that in some cases headache may be precipitated by overdosage with a treatment extract.[4] The importance of bacterial infection or sensitization in many chronic cases must be recognized.

Incidentally, it is also my opinion that headaches other than the frontal type may occasionally be associated with inhalant sensitizations.

It is well recognized that the syndrome migraine may be produced by sensitization to foods. Other headaches which do not present the criteria of classical migraine may also be produced by the ingestion of foods. While the sensitization may be to a rarely eaten food, it is very often due to a food which is ingested commonly. Headache may be caused by overindulgence in such a food. I feel that skin testing, though of limited value, should be done. Direct tests should be made after the food has been avoided for several days in order to prove whether or not sensitization is clearly present. In some cases, it may be advisable to mask or hide the addition of the suspected food to the diet in order to lessen the possibility of mental influences.

At times, in the same individual, headache may be caused by sensitization to inhalants as well as to foods.

I feel that the allergist should not neglect the recognition of any psychogenic factors. In the optimal situation, organic pathology is first ruled out by the internist or the neurologist. Refraction may also be necessary. The psychiatrist and allergist working together may be able to control the complex factors that may enter into the causation of allergic headaches. Such teamwork is not necessarily dependent on the use of a large headache clinic. Also, the allergist as part of his management of the case may really provide a more or less directive form of psychotherapy. The patient may be helped by such therapy which is active and positive in na-

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CAFERGOT SUPPOSITORIES IN MIGRAINE

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THE management of the acute migraine attack has recently been simplified. This has developed out of clinical studies directed along two channels. The first approach demonstrated the synergistic effect of caffeine with ergotamine tartrate as a vasoconstrictor in migraine. Other developments proved that this combination could be effectively self-administered by mouth or by rectum in the acute migraine attack. The fruits of these studies were Cafergone tablets[5,6,8,9,11] and Cafergot suppositories.[1,3,7]

A preliminary paper,[1] published early in 1950, recorded our early favorable experience with ergotamine-caffeine suppositories in migraine. Reports by Cohen and Criep[3] and Kadish[7] have also appeared, which likewise record favorable results obtained in several headache conditions using a variety of oral and rectal ergot alkaloids in combination with caffeine. Data has been analyzed in our latest series of cases which confirms our initial reports in migraine. Some discrepancy exists, however, in the value of these agents in the treatment of tension headache. Our results in eighty-two cases of headache treated with rectal suppositories of ergot and caffeine are herewith presented.

METHODS AND MATERIALS

Patients with migraine were seen at the Headache Clinic at the George Washington University Hospital and in private practice. Each case was investigated thoroughly as previously described.[2] In many cases response to Gynergen, DHE and Cafergone was known. Following complete discussion of the nature of their illness, the patients were instructed to use a suppository as soon after the onset of a headache as possible. The usual dose was one suppository. If relief did not occur in one hour, an additional suppository might be inserted. If reactions were too violent, the next headache was to be treated with one-half suppository.

The preparations for our study were furnished by the Sandoz Pharmaceuticals Company through the courtesy of Mr. Kenneth Ericson. These were:

Cafergot (EC 112)—2 mg ergotamine tartrate and 100 mg caffeine.
ECB 115—2 mg ergotamine tartrate and 100 mg caffeine and 0.25 mg Bellafoline substance.
EC 222—2 mg ergotamine tartrate and 200 mg caffeine.

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TABLE I. EFFECT OF CAFERGONE SUPPOSITORIES IN HEADACHE

Drug	Diagnosis	Number of Patients	Results† Excellent	Good	Poor
EC 112	Migraine	27	21	5	1*
(Cafergot)	Tension	5	1	1	3
ECB 115	Migraine	29	25	3	1
	Tension	6	1	1	4
EC 222	Migraine	13	12	0	1*
	Tension	2	0	0	2
Totals	Migraine	69	58	8	3
	Tension	13	2	2	9

* Medication not retained.
† See text for criteria of results.

CRITERIA OF RESPONSE

The following criteria, similar to those used by Horton,[6] have been adopted:

Excellent—Almost complete relief within four hours.

Good—Substantial improvement in four to eight hours or 50 per cent improvement in four hours.

Poor—Less than 50 per cent improvement or relief after eight hours.

RESULTS

The results obtained in patients with migraine and tension headaches, using various agents, are recorded in Table I. Over-all results indicate excellent results in fifty-eight of sixty-nine migraine patients (84 per cent), as opposed to excellent results in two of eleven tension headache patients (eighteen per cent). There seems to be little preference in the various preparations used as regards potency. Results were manifest in excellently responding cases in as quickly as twenty minutes, and the majority had decided relief within two hours.

The dosage of the Cafergone suppository, expressed in mg of ergotamine tartrate in the fifty-eight "excellent cases" is tabulated in Table II. The vast majority of patients respond fully to 2 mg (one suppository). Where undesirable side effects occurred on this dosage, patients were advised to use one-half suppository (one mg), with success in three cases. Only one in ten patients required 4 mg to effect excellent relief. What has not yet been determined is whether the eleven patients who gave fair or poor results would have done better on larger dosage.

The side effects of Cafergone suppositories are directly attributable to the presence of ergotamine. Of the thirty-five patients (these are tabulated in Table III) experiencing nausea and vomiting following medication, twenty-eight of these regularly or frequently experienced these symptoms in untreated attacks. The severity of nausea and vomiting was increased over the control in a few patients, but gastrointestinal upset was sufficiently severe to discontinue medication in only one case. The two instances of diarrhea occurred within fifteen minutes and were sufficient to cause lack of absorption. These two cases are included in the treatment failures (Table I). The one case of facial rash probably represented an instance of

drug idiosyncrasy, since the same effects (along with weakness, leg and abdominal cramps, and palpitations) occurred in this patient with gynergen and DHE parenterally. Comparative results indicated that the lowest incidence of trouble occurred with Cafergot (EC 112) and the highest with EC 222. The addition of Bellafoline did not materially decrease the incidence of gastrointestinal upset.

TABLE II. DOSAGE OF RECTAL ERGOTAMINE IN 58 SUCCESSFULLY TREATED MIGRAINE PATIENTS

Dose	Number	Per Cent
1 mg	3	5
2 mg	49	85
4 mg	6	10
6 mg	0	0
Totals	58	100

TABLE III. SIDE EFFECTS IN 82 PATIENTS TREATED WITH ERGOT-CAFFEINE SUPPOSITORIES

Symptom	Number	% of Total
Nausea and vomiting	35*	43%
Weakness	6	7%
Diarrhea	2	2%
Leg cramps	2	2%
Abdominal cramps	2	2%
Palpitation	2	2%
Facial rash	1	1%

* Twenty-eight of these reported nausea and vomiting to be a routine accompaniment of the regular migraine attack whether or not ergot was used.

Most patients who used oral and rectal Cafergone preferred the rectal route because of the uniformly good results rectally as opposed to the inconstant effects dependent upon upper gastrointestinal absorption. In cases where DHE had been previously used with success, this agent was preferred parenterally in a few cases because of decreased incidence of side effects. Most of our patients, however, preferred the ergotamine suppositories to DHE administration. Only one patient preferred Gynergen parenterally, whereas three preferred the rectal form to the injections.

DISCUSSION

Our results indicating excellent results in 85 per cent of migraine patients are in accord with other studies[10] on ergotamine in this condition. Some discrepancy, however, exists when comparing our results (two of eleven excellent) in tension headaches, with the findings of other investigators. Thus Horton[6] found excellent results in five of eleven cases, and Kadish,[8] using similar criteria, obtained excellent results in forty-nine of sixty cases with tension headaches.

Part of the difficulty has been a lack of general agreement as to the exact

definition of the various types of headache. It is our opinion that migraine and tension headaches represent different types of pain reaction. In the former, the end organ of pain lies in the extracranial branches of the external carotid artery. The stimulus for the production of this pain is usually, in order of freqency, psychogenic, endocrine (menstrual, menopausal, et cetera) or allergic. The clinical picture is basically the same in most patients. The features common to all patients are as follows:

1. Periodicity of attacks, most clearly demonstrable in the early stages of the disease.
2. Hemicephalgia—pain is usually unilateral, most frequently involving the same side in subsequent attacks, but occasionally the opposite side. As the headache persists, the pain may become generalized throughout both sides of the head.
3. The pain is pulsatile, variously described as "beating," "pounding," "throbbing," or "thumping."

Additional features of this condition, but by no means invariable, include:

1. Aura consisting of scotomata, hemianopia, photophobia, paresthesias. paralysis, numbness, and other central nervous system phenomena.
2. Nausea and vomiting, frequently attending the migraine attack. allergy.
3. A positive family history of migraine and occasionally of epilepsy and

Additional points of interest include the fact that favorite locations for the headache are the temporal, supraorbital, retrobulbar, and parietal regions. Less frequently pain may be postauricular and occipital. The duration of the headache is usually from twelve to seventy-two hours. Migraine attacks most frequently occur premenstrually and abate during pregnancy. Another diagnostic criteria, but obviously unsuited to our present purposes, is the uniformly good response to ergot alkaloids.

The pain in muscle-tension headaches, in contradistinction to the above description, originates most frequently in skeletal muscle. The pain is usually the result of sustained muscle tension which develops in "tense, dissatisfied, apprehensive, anxious people."[12] The headache in these cases offers the following features:

1. Occasionally periodic, but more frequently irregular and often continuous if the anxiety is established.
2. Pain is seldom unilateral. Most frequently the pain is bioccipital, vertical or bifrontal.
3. The pain is seldom throbbing. The pain is perceived usually as a constant pressure sensation. Expressions frequently used to explain this

type of pain are "head caught in a vise," "scalp on too tight," "top of my head blowing off." Patients with occipital and nuchal pain frequently extend the head on the neck, stroking the neck muscles, when asked to locate the pain.

4. Prodromata are invariably absent. Nausea and vomiting rarely develop. The family history is usually negative for headaches, epilepsy or allergy. The pain may last for days, weeks, months or years.

Horton[6] applies the term "tension headache" to a type of head pain which follows upon a sustained period of nervous tension. In these cases pain develops as a result of vessel hypotonicity, "vascular fatigue." This type of occurrence, we feel, more properly fits into the category of vascular headaches, of which migraine is the prototype. These cases would be expected to respond to ergot alkaloids in good, but less dramatic, fashion.

Confusion arises on other scores. The clinical pictures described in some detail above represent classical examples at either end of two dissimilar poles. In between fall some people with both components. Most patients with migraine, if allowed to go on for days, will develop sustained muscle tension with additional headaches. Any one patient may at different times develop either type of headache, each of different severity and duration and each requiring different treatment. It is essential that the predominant feature be determined in all cases, since ergotamine, when administered, is usually ineffective in continuous headache states, and if given over prolonged periods of time may produce serious toxic effects.[4]

SUMMARY

Cafergot, a suppository consisting of 2 mg of ergotamine tartrate with 100 mg of caffeine, is most effective and conveniently self-administered in the large majority of migraine patients. Serious side effects are unusual in this low dosage of ergotamine. The results in tension headaches have proved disappointing in our series, thus emphasizing the need for care in diagnosis and classification in the individual headache problem. Criteria for differentiation are given in some detail.

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TROPICAL EOSINOPHILIA AND ITS POSSIBLE RELATIONSHIP TO LOEFFLER'S SYNDROME AND PERIARTERITIS NODOSA

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AN INTERESTING condition has recently attracted much attention in Ceylon, India, and abroad. Different writers have described this clinical syndrome under different names: viz., pseudo-tuberculosis condition associated with eosinophilia,[4] tropical eosinophilia,[15] benign eosinophilia, leukemia,[12] eosinophilic lung,[2] pulmonary acariasis,[13] pulmonary eosinophilosis.[14]

The purpose of this paper is to set forth the various manifestations of tropical eosinophilia, to briefly review the two conditions Loeffler's syndrome and periarteritis nodosa, and to indicate that vascular allergy forms the basic mechanism of these three seemingly different clinical entities.

Tropical eosinophilia is characterized by persistent and intractable cough, paroxysms of dyspnea, and a high total leukocyte count, with persistent and absolute eosinophilia and mottled shadows in the lungs. It responds well to arsenical therapy.

Loeffler[9] described the syndrome known by his name as characterized by transient, migratory pulmonary infiltration associated with peripheral eosinophilia, and producing little or no constitutional disturbance and requiring no special treatment.

The clinical pattern recognizable in periarteritis nodosa is a protracted and pyrexial illness, with limb pains, visceral disturbances taking the form of asthma, pneumonia, and cardiac and renal disease, occasionally subcutaneous nodules and eosinophilia in the peripheral blood.

Recovery is not uncommon. It has no particular line of treatment.

INVESTIGATIONS

Clinical.—The history consists of an accurate, detailed, and chronologically recorded compilation of all symptoms from infancy to the time of consultation. It is common for the patients to lose sight of the early symptoms when the disease has lasted for some time. Emphasis is laid on the mode of onset, environmental conditions, occupation, personal or family tendency to allergic disorder, and pulmonary tuberculosis or other respiratory diseases.

Laboratory.—

1. Examination of sputum for tubercle bacilli. The search for mites was undertaken in fifty consecutive cases and had to be

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abandoned, as it yielded negative results and as it was a time-consuming process.

2. (a) Examination of blood for total white cell count, and differential count in the peripheral blood. (b) Cold agglutination tests (carried out in doubtful cases).
3. Examination of feces for helminth ova, amebae, cysts and parasites.
4. Radiological examination of chest and air sinuses.

TABLE I

	Tropical Eosinophilia		True Asthma	
	Male	Female	Male	Female
0-5	10	9	28	21
6-10	35	31	39	27
11-15	30	27	112	37
16-20	34	30	72	49
21-25	47	27	121	52
26-30	64	31	152	41
31-35	51	33	84	64
36-40	36	29	140	44
41-45	36	19	116	33
46-50	37	23	86	43
51-55	20	13	97	38
56-60	11	7	64	16
61-65	6	6	19	8
66-70	3	6	6	7
	420	286	1136	480

The clinical material consisted of 912 cases collected from the following sources during a period of eighteen months:

Asthma Clinic ..... 706 Cases
Medical Wards and Out-Patients ..... 206 Cases

It should be mentioned that patients who attended the clinic were those with frank asthmatic attacks or troublesome dyspnea. Patients with only a cough rarely found their way into the clinic. They were referred from the Antituberculosis Institute for Medical Outpatients.

Diagnosis.—The diagnosis of tropical eosinophilia was made on the following criteria:

A history of an illness with long continued cough, dyspnea, nocturnal wheezing, a high total white cell count of over 4,000 per cmm, with an eosinophilic count of over 20 per cent, and mottled shadows in the x-ray of the lung constitute sufficient evidence to establish a diagnosis of tropical eosinophilia.

Etiology.—No race seems to be exempt. While the patients attending the clinics are drawn largely from those with small and moderate means, persons of every social class seem to be affected by this disorder.

Age.—The age of onset varies widely from the age at which the patient seeks treatment. Only 12 per cent of cases sought medical attention within a week. In a large proportion of cases, there was an interval of four or five years, sometimes extending on to twenty-five.

TABLE II

	Age	Duration of Asthma	Other Allergic Diseases	Clinical Examination	X-ray	Total W.B.C.	E%	Treatment	Remarks
Father:	48 Years	9 Years	Nil	Rales & rhonchi	Chronic bronchitis	8400	21%	Carbarsone ineffectual asthma not cured in spite of treatment.	A case of true asthma.
Child: —	4 Years	2 Years	Nil	—	Bilateral coarse mottling; antral opacities.	21800	50%	Carbarsone produced cure.	A case of tropical eosinophilia.
Child: —	1 2 — 12 Years	3 Days	Nil	Broncho-spasms, Rales ++ Rhonchi ++	Not done	25000	59%	-do-	A case of tropical eosinophilia.
Child: —	5 Years	1½ Years	Nil	Tonsils enlarged and septic.	—	12400	16%	Septic tonsils removed and a course of penicillin given—asthmatic condition improved.	True asthma

The youngest patient on record was five months, and the oldest seventy-five years of age.

Table I shows the age grouping of 706 cases of tropical eosinophilia attending the Asthma Clinic, and that of true asthmatics. It will be seen that the age incidence is the same in both types, reaching their peaks at about twenty-seven in the male, and at about thirty-five in the female.

Familial.—There were eighty-eight families in which more than one member had been subject to tropical eosinophilia. Asthma was the chief symptom in all. In three families, some of the members were subject to true asthma, while others had manifestations of tropical eosinophilia.

An instance of this in one family is summarized in the following table, in which the chief features are tabulated. It can be seen that the father and the daughter were subject to true asthma, while the two sons showed features of tropical eosinophilia.

Occupation.—Several writers, Carter et al,[1] Soysa and Jayawardena,[13] Jhatakia,[7] have stressed the importance of dusty occupations as an etiological factor. This is not corroborated by the present work. No special type of work can be singled out as predisposing to the development of eosinophilic bronchitis.

Locality.—Crowded localities and certain inland areas furnished the largest number of cases, an observation contrary to that of Weingarten,[15] who recorded a high incidence in those living in proximity to the sea.

TABLE III. SUMMARY OF THE CLINICAL TYPES OF TROPICAL EOSINOPHILIA

Pulmonary	History	Physical Examination	Laboratory Investigations				E.S.R.	Radiological	Treatment
			Total W.B D.	E%	Sputum for T.B.	Stools for Amebae Cyst and Ova.			
Case No. 1 Asthma G.R.,Male 27.	Irritable and unproductive cough followed after some days by dyspnea and asthmatic paroxysms, malaise, lassitude.	Temperature normal throughout the illness, expectoration scanty and mucoid. Harsh breath sounds and prolonged expiration accompanied by rhoneni of varying pitch.	24700	47	Nil	Nil	—	Diffused mottling of lungs.	Treatment with injections of neoarsphenamine; exacerbation of symptoms on third day. Rapid relief subsequently.
Case No. 2 Pleurisy A.F.,Male 38.	Cough, fever and breathlessness of 10 days' duration.	Temperature 100°; signs of effusions over night base.	24000 Aspirated fluid showed large number of eosinophils.	84	Nil	—	Slightly raised.	First X-ray showed moderate sized effusion. Second X-ray three weeks later showed lung fields normal with slight thickening of pleura.	Treated with injections of neoarsphenamine.
Case No. 3 Pneumonia J.S., Male 24.	Fever, cough and pain in the chest of 3 days' duration.	Temperature 104°, P.110, R. 46. Sputum blood-stained. Lungs showed diminished air entry of left base with crepitations.	21600 two weeks after treatment 8400	45 7	Nil	—	—	—	Treated with penicillin and carbarsone tablets.
Case No. 4 Pseudo-tuberculosis Rev. B.M.T. 48.	Cough, fever, 3 weeks, loss of appetite.	Temperature varying between 99 and 101°; expectoration mucopurulent. Lungs: harsh breath sounds over left apex with crepitations.	13600 after treatment 7800	66 8	Nil	—	First hour 27 Second hour 46	Appearances suggestive of bilateral T.B. Two weeks after specific treatment lungs showed normal appearance.	Fever subsided 3 days after treatment with carbarsone. Second course after fortnight, disappearance of all symptoms. Third course was needed to bring blood count to normal.
Case No. 5 Hemoptysis S.M., Male 34.	During the fortnight preceding he had coughed out blood twice; previous health excellent.	No abnormality of lungs or heart. Temperature normal, general health good.	32000	34	Nil	—	First hour 14 Second hour 24	Mottling of both lungs.	Treatment with neoarsphenamine.
Case No. 6 Cardiac type P., Male 27.	Attacks of substernal pain, dyspnea, sweating and prostration which used to last for an hour or so.	Fever for 2 days. P.90. Lungs: clear. Heart: no apparent abnormality. B. P. 130/80.	14800	32	—	—	—	Screening of heart, no abnormality. E.C. G.T2; inverted lungs fields—clear.	Treated with sedatives and carbarsone; blood returned to normal within a fortnight. No recurrence of symptoms.
Case No. 7 Intestinal type W.R.S.N., Male 29.	Frequency of stools containing blood and mucus of 6 weeks' duration; warded before for treatment of eosinophilia bronchitis.	Furred tongue; diffuse tenderness of abdomen.	14000	75	—	Nil culture negative for specific organisms negative.	— —	Chronic bronchitis.	Treated successfully with neoarsphenamine. No other measures adopted.
Case No. 8 Continued pyrexia K.P.F.P., Male 22.	Continued fever of 12 days' duration.	Temperature varying from 100 to 102°. P.110. Lungs: clear; heart: normal; abdomen: soft; liver: normal; spleen: normal	15000 blood for widal neg. Blood culture: Nil.	62	Nil	—	—	No abnormality.	Treatment with carbarsone Temperature subsided within 3 days.

In fact, the incidence of the disease among the seacoast residents appears to be exceedingly small.

GENERAL DESCRIPTION OF THE DISEASE IN ADULTS

In the vast majority of cases the illness is preceded by an infection of the upper respiratory tract. The disease has an insidious onset and is ushered in by bouts of irritable and unproductive cough. These become progressively more frequent and troublesome, particularly at night, producing a considerable degree of malaise and lassitude. It is usually accompanied by an aching pain behind the upper part of the sternum. Fever is occasionally present and is of a moderate degree. Expectoration is scanty and mucoid. This stage lasts for three to ten days. Dyspnea now sets in after each bout of cough or after exertion and is soon followed by paroxysms of asthma.

In 15 per cent of cases the disease does not progress beyond the stage of cough and is frequently missed until a blood count is made. These cases frequently seek treatment at a tuberculosis dispensary or medical outpatients' department. In a few instances the disease is mild and disappears without any form of treatment. These represent the abortive type and are recognized on routine health examinations. In the untreated case, there are recurring paroxysms of cough and dyspnea at varying intervals with some degree of deterioration of health. Many suffer from frequent asthmatic seizures differing in no way from those due to true asthma and continuing for a number of years.

Acute types are rarely met with. These may take the form of pleurisy, pneumonia, pseudotuberculosis, hemoptysis, anginal seizure, dysentery, continued fever, periarteritis nodosa.

Arsenical therapy results in prompt arrest of the disease.

CLINICAL CLASSIFICATION

1. Abortive type.
2. Acute
   - Pleuritic
   - Pneumonic
   - Pseudotuberculosis
   - Hemoptysis
   - Cardiac
   - Intestinal
   - Continued pyrexia
3. Chronic asthmatic.

Typical cases illustrating the clinical features in each of these types are set forth in Table III.

TROPICAL EOSINOPHILIA IN CHILDREN

There were eighty-five patients in this series. Their ages ranged from infancy to the tenth year. The incidence was highest in the first year. These offered a special problem. They had been treated on different occasions

for bronchitis, bronchopneumonia or pneumonia. The relief had often been prompt but incomplete. The treatment invariably had been by penicillin or by sulfa drugs. The blood count was usually omitted owing to the urgency of the case.

A conspicuous feature is the difference in the mode of onset and the clinical features usually met with in the adult. The unproductive, harassing cough and the pain behind the sternum that herald the onset of tropical eosinophilia in the adult is not witnessed in the child.

Three different clinical types may be recognized.

1. *Recurrent Bronchitis Type.*—There is a pyrexia rarely exceeding 102° with little or no cough. Dyspnea is the most prominent symptom. Physical signs are those of bronchitis. This type recurs at the onset of a cold or as a result of exposure to cold weather and is constantly met with in the first year.

2. *Coryzal Type.*—In the fourth and fifth years, a common mode of onset is the involvement of the upper respiratory tract. Here the patient complains of sore throat, cough, and sneezing which last a day or two. This is followed by an asthmatic paroxysm. Slight pyrexia accompanies the illness.

3. *Bronchopneumonic Type.*—In the latter part of the decade, it is often the sequel of a pulmonary complication resulting from whooping cough, measles, or pneumonia. Fever, cough, and dyspnea supervene rapidly, and the condition is frequently diagnosed as bronchopneumonia until the blood examination is made. Recurrences are frequent. X ray shows peribronchial fibrosis in addition to mottling. The condition rapidly improves with penicillin, though arsenic is needed to restore the blood condition to normal and for a complete control of the disease.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis it is necessary to exclude a number of tropical conditions, e.g., heminthiasis, filariasis, which show a high degree of eosinophilia, pulmonary tuberculosis, bronchomycosis and pneumoconiosis, coccidioidomycosis before one arrives at a diagnosis. In true asthma, the total white-cell count is rarely above normal and the degree of eosinophilia is slight. The blood count, on which emphasis is placed for purpose of diagnosis, presents many variations. In some instances the percentage of eosinophils remains high with a slightly raised white-cell count. In others the total white-cell count is high but the percentage degree of eosinophils is only moderately raised. The severity of the associated infection and the degree of sensitivity probably determine the blood picture at any given time.

Occasionally, cases are encountered where one examination shows a

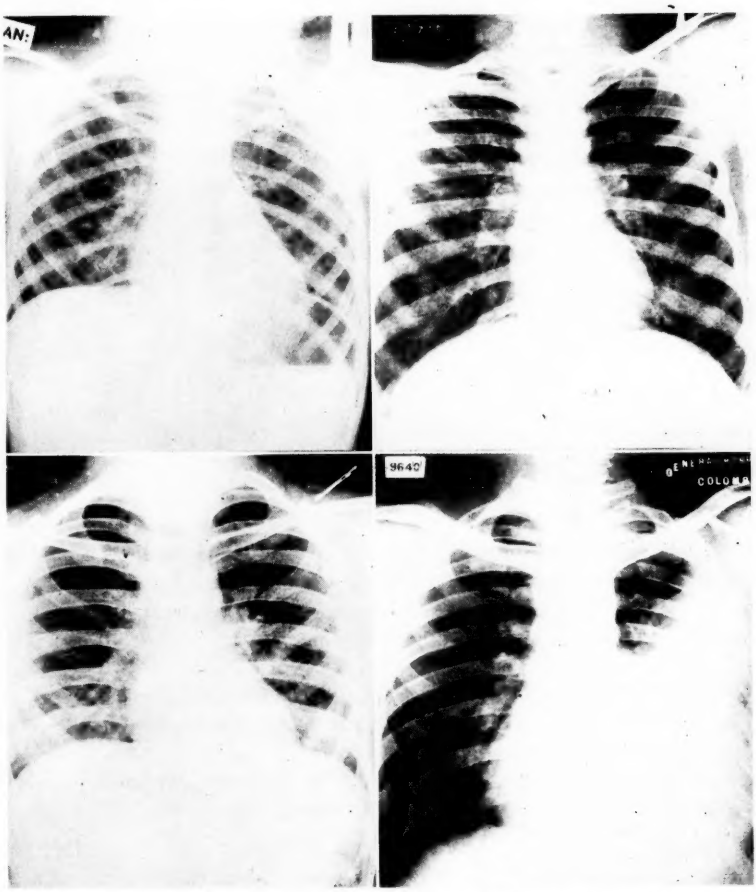

Fig. 1. Typical ground glass appearance.

Fig. 2. Miliary mottling of both lungs.

Fig. 3. Vascular accentuation extending to periphery.

Fig. 4. Pleural effusion.

leukocyte count suggestive of a true bronchial asthma, while a subsequent count affords evidence of tropical eosinophilia. The following case illustrates this:

C.D.C.M., eight years, has had asthma for seven months. Grandfather had been subject to asthma. Blood count on July 27, 1949, total white blood count, 8,800; polymorphonuclears, 48; leukocytes, 36; eosinophils, 16. On October 24, 1949, total white cell count, 12,400; polymorphonuclears, 48; leukocytes, 19; eosinophils, 36.

It is a noteworthy fact that the splenic enlargement noted by several writers (Weingarten,[15] Viswanathan[14]) has not been met with in this series.

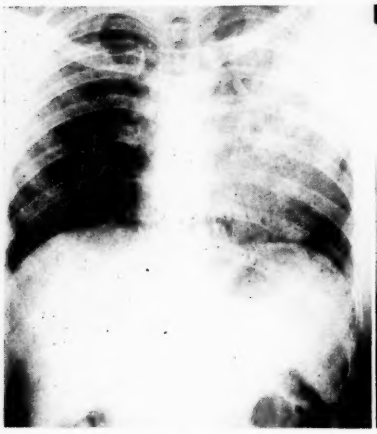

Fig. 5. Pneumonic type.

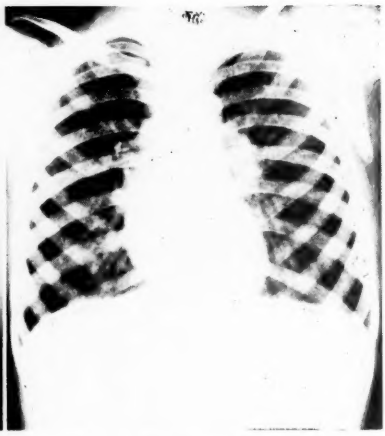

Fig. 6. Peribronchial fibrosis.

RADIOLOGICAL FINDINGS

Chest.—The radiological shadows in tropical eosinophilia show a marked degree of variability. They may assume any one of the following features or a group of them or may even show the normal architecture of the lung though the eosinophilic counts may be high.

Ground glass haziness of the involved lung
Coarse or fine reticulation
Miliary mottling of both lungs
Vaguely outlined irregular or partly confluent patches
Bronchopneumonic or pneumonic consolidation
Peribronchial fibrosis
Pleural thickening or effusions
Vascular nodulation
Vascular accentuation extending to periphery
Prominent hila

The commonest picture in tropical eosinophilia is the ground glass appearance produced by an exudate into the alveoli. This gives a classical appearance in most cases. The opacity takes the place of the normal air shadows in the alveoli. The distribution is not characteristic but is commonest on the right and in the lower two-thirds of the lung. This may be called the alveolar exudative type of lesion. Nodulation along the blood vessels is seen in a small percentage of cases. This again produces a miliary mottling. The miliary shadows are two to four mm diameter and appear of uniform density as opposed to the miliary mottling seen in the miliary tuberculosis with a denser centre and blurred periphery. But with alveolar collapse the mottling shows an appearance similar to

that seen in miliary tuberculosis. The miliary shadows are not confined to the bases but may extend to the apices. The vascular nodulation is seen mostly in the small vessels outside the hilar region. Even if all other features are not present, a great majority will show prominent vascular

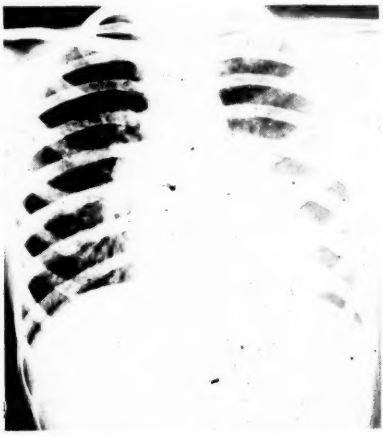

Fig. 7. Vascular nodulation.

markings extending to the periphery and peripheral reticulation. Both coarse and fine reticulation are seen, but the latter is commoner.

In the stage of regression prominent hilar truncal markings are seen.

In children the picture suggests that the disease spreads from the hilum. There is a flaring out of the hilar shadows in a fan-shaped fashion with prominent vascular markings and fine mottling of the lungs fields; occasionally hilar glands are involved, although in adults it is never present.

Air Sinuses.—In 41 per cent of cases, there was evidence of sinusitis.

TREATMENT

A very satisfactory feature in this syndrome is the eminently successful response to arsenical therapy, which is now universally recognized. In view of the involvement of air sinuses and tonsils in some cases, a necessary adjunct to this therapy is the eradication of the septic foci by appropriate measures. Some cases that did not respond dramatically to this arsenical therapy in the early cases of these series were found to be those complicated by sinus or tonsil infection.

Suitable course of treatment is neoarsphenamine in doses of .15 gm. to 0.3 gm dissolved in 10 cc of cold, sterile distilled water and given intravenously at intervals of a week for eight to ten weeks. Since this treatment was given at the Out-Patient Department, much care had to be exercised. The dosage is smaller than is usually recommended.

Instead of intravenous injections, oral administration of pentavalent arsenical may be employed. For an adult a tablet of carbarsone twice a day for ten days may be given. The reduction of the white cell count and eosinophilia does not occur so rapidly as the amelioration of the symptoms. These disappear in the reverse order of their occurrence. Asthmatic seizures and dyspnea rapidly subside, while cough is the last to disappear. Exacerbation of the symptoms with eosinophilia commonly occurs after the first injection. More than one course of treatment with arsenic is sometimes necessary to bring out a lasting improvement.

LOEFFLER'S SYNDROME

Loeffler[9] first called attention to a clinical syndrome characterized by transient and migratory pulmonary infiltrations, by the comparative absence of symptoms and physical signs, and by the presence of an eosinophilia ranging from 10 to 60 per cent. There is little or no fever, and the general condition remains practically normal. The lung condition rarely lasts longer than a day or two. The diagnosis is usually made by x-rays. While Loeffler was of opinion that various etiological conditions were responsible for this syndrome, Engel[3] attributed it to an allergic state brought about by inhalation of privet pollen and termed it "oedema allergicum pulmonalis." The privet asthma, as he called it, begins with headache, moderate fever, and cough. The physical findings are slight, and x-ray shows discrete shadows spread over an entire lobe. The lung condition clears up within a day or two. Numerous similar cases have been described, particularly in children, less frequently in adults. Parasites have been found in these. The pulmonary manifestations were considered by these authors as an expression of allergy.

TROPICAL EOSINOPHILIA WITH FEATURES RESEMBLING LOEFFLER'S SYNDROME

In the routine examination of chests of new entrants for Government Service, six cases were seen. They had been in good health right up to the time of examination and had not suffered from any chest complaint. They showed the characteristic blood and also the characteristic x-ray pictures. In a health survey of university students of this country, four out of twenty-six students who gave even the remotest history or showed signs of eosinophilia bronchitis showed the typical radiological picture and high eosinophilia. As in Loeffler's syndrome, the lung signs and eosinophilia were transitory and the recovery rapid and spontaneous.

Periarteritis nodosa.—Kussmaul and Maier,[8] described the disease of the arterial walls presenting a peculiar but characteristic histological appearance and accordingly termed it periarteritis nodosa.

Gruber[5] stressed the fact that periarteritis nodosa is not a disease entity, but it is to be regarded as a hyperergic expression involving portions of the arterial walls of one or more organs that have become sensitive

during the course of a prolonged infectious disease. The experimental studies of Rich and Gregory[11] have demonstrated that widely different types of sensitizing antigens are capable of causing periarteritis nodosa.

Harkavy[6] has reviewed the pathogenesis of bronchial asthma with recurrent pulmonary infiltrations and eosinophilic polyserositis and is convinced that the vascular apparatus plays a basic role in the problem of altered tissue reactivity in man.

From the observation which he has recorded he infers that the manifestations depend on the different responses of those organs in which the primary sensitization of blood vessels plays the determining role.

A PROBABLE CASE OF TROPICAL EOSINOPHILIA WITH PERIARTERITIS NODOSA

G.M., male, aged seven, was brought by his mother to the Out-Patient Department because he was limping. Two weeks prior to this the child had developed fever and pain in the right forearm. Two boils described by mother as "blood boils" cropped up in this region. These burst, letting out a thick sanguineous matter, but the fever continued. A week later he found he could not straighten out his knee. He was referred to the surgeon, who detected a small lump in the left gastrocnemius. Examination of the blood revealed total white-cell count 18,000 per cmm, polymorphonuclears, 36 per cent; leukocytes, 22 per cent; eosinophils, 42 per cent. In view of the high eosinophilic count, the chest was x-rayed. This disclosed mottling of the lung, characteristic of tropical eosinophilia. The blood pressure gave normal readings and the urine showed no abnormality. There was no evidence of trichiniasis or filariasis. Biopsy of the lump was not permitted.

The child was treated with carbarsone only. The painful lump disappeared in six days. Four weeks later, the child had shown considerable improvement in his general health. X-ray of chest showed no evidence of infiltration. Blood picture was total white blood count, 7,200; polymorphonuclears, 36; leukocytes, 56; eosinophils, 8.

Discussion.—It will be seen from the Table III that although these cases satisfied the criteria necessary for the diagnosis of tropical eosinophilia the clinical manifestations suggested the involvement of one particular system more than another, thus giving rise to several clinical types of the disease. The maximum effects appear to have been produced in the lungs; and even here the pathogenetic agent has shown a peculiar type of tissue predilection affecting in some cases bronchi, in others the pleura and also groups of alveoli. The nature of the underlying pathology can only be surmised in the absence of an opportunity to study the changes in the tissues. The occurrence of hemoptysis, the presence of blood in the stools in the intestinal type, the characteristic radiological features, viz., exudates, prominent vascular markings, vascular nodulations, definitely indicate some form of vascular damage. The onset of substernal pain with characteristic electrocardiographic findings suggests cardiac ischemia brought on by some form of vascular lesion, and a pneumonic or a pleuritic lesion indicates some change in the vessel walls which has caused an increase in its permeability resulting in the local escape of vascular contents.

Although the clinical picture showed a wide degree of variations, there was one feature which was common to all the various clinical manifestations: namely, a considerable rise in the eosinophils of the blood. It is now generally accepted that the rise in eosinophils signifies the response to a foreign protein, and therefore it is reasonable to presume that we are here dealing with that type of response which has primarily affected the peripheral vessels. In other words, this is an allergic condition affecting the blood vessels of the lungs in most cases and those of the heart and intestines in others. In fact, any organ of the body may become sensitized. Thus simultaneously or alternately with paroxysms of asthma there may be cardiac, intestinal or other visceral manifestations.

Whether the sensitizing agent is a mite, a virus, or a bacterium remains unproven. Indeed it is a difficult matter to incriminate any one of these, as associated infection, especially in the lungs, always raises the question of the part played by viruses and bacterial proteins in the production of the allergic state.

The relationship of tropical eosinophilia to the other two conditions, viz., Loeffler's syndrome and periarteritis nodosa, remains now to be discussed. The former is often a symptomless state but shows a high degree of eosinophilia. The latter is a form of necrotizing inflammatory panarteritis, but eosinophilia is not always present. Four cases of the former in routine medical examination of new entrants to the Government Service and two probable cases of the latter associated with asthma were seen. In all these cases the common features were the presence of a very high degree of eosinophilia and the remarkable response to arsenical therapy, as revealed by the disappearance of the symptoms in the latter. It would therefore appear that the three diseases, viz., tropical eosinophilia, Loeffler's syndrome, and periarteritis nodosa, are but different manifestations of a single pathological condition which has for its basis the sensitization of the blood vessels to some allergen. Loeffler's syndrome is probably an example where the effects of such sensitization are minimal and exercised exclusively on the pulmonary vessels. Tropical eosinophilia probably represents allergic manifestations with a more widespread involvement of the blood vessels. The degree of involvement in different situations shows remarkable variations, thus giving rise to different clinical manifestations depending on the site which is predominantly involved. The nature of the change in the vessel walls in the two conditions is not obvious, as it has not been possible to examine such vessels. The complete recovery in every case suggests that the change is mild and reversible. In periarteritis nodosa is seen as example of a maximum response of the vascular tissues to an allergic stimulus. The change in the vessel wall in this case in irreversible, and the repair of the damage to the vessel necessarily leaves a scar which marks the site of original involvement.

SUMMARY

Cases of Loeffler's syndrome, tropical eosinophilia exhibiting different clinical types, and periarteritis nodosa have been described. These three conditions are but different manifestations of a single pathological process which has as its basis the sensitization of blood vessels to an undetermined allergen. In the large majority of cases, cough and bronchitis form the chief manifestations, frequently associated with pulmonary infiltrations as revealed by x-ray. The typical blood picture may occasionally show variations. The vascular reactions in some instances become more generalized as shown by cardiac, intestinal, and skin lesions. The mildest type resembles Loeffler's syndrome. These show no symptoms and are detected in the routine examination of chest in health surveys; periarteritis nodosa, on the other hand, represents the severe phase of the disease.

The identity of the basic mechanism illustrates that Loeffler's syndrome, the commoner manifestations of tropical eosinophilia, and periarteritis nodosa are merely gradations of hyperergic vascular response.

The primary etiologic agent of each of these remains unproven.

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OCCURRENCE OF BACTERIAL RESPIRATORY INFECTIONS RESEMBLING EPIDEMIC CORYZA IN ALLERGIC PATIENTS

Etiology and Treatment

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AFTER extensive studies of the common cold, Dochez et al (1924-1936) concluded that epidemic coryza was caused by a filterable virus.[3] Strains of virus recovered from filtrates of nasopharyngeal washings obtained during the initial stage of infection were grown and transferred through chick embryo tissue cultures[1,2] and through intact embryos by implantation on the chorioallantoic membrane.[7] The filtrates from the nasopharyngeal washings, the fifteenth passage through tissue cultures, and the virus after three transplants in the intact embryo caused colds in volunteers inoculated intranasally. Some of these observations have been confirmed.[8,9,16]

In studies of the bacterial flora of the adult nares and nasopharynx, Shibley, Hanger and Dochez found no evidence that any one species might be responsible for the initial stage of infection.[10] Cultures made during colds were not found to be remarkably different from those made in the intervals between infections. In infants[5] the upper respiratory tract was found to be sterile at birth and gradually to acquire the nonpathogenic organisms and then the potential pathogens found in the adult flora. With the acquisition of this flora[6] the character of the colds in infants changed, assuming the characteristics of the adult cold with an initial rhinorrhea and a secondary purulent stage. Although no one species seemed to initiate colds in infants and young children, in a group with recurrent colds *Diplococcus pneumoniae* and *Haemophilus influenzae* were especially prominent. In adults hemolytic streptococci, staphylococci and *Haemophilus influenzae* appeared to be prominent as late or secondary invading organisms.[10]

ALLERGIC FACTOR IN BACTERIAL COLDS

Epidemiologic data collected from 1933 to 1945, to be published elsewhere, are the basis for the belief that visible pathogens may cause colds, uninitiated by virus infection, in allergic patients. The essential observations are summarized here to establish the fundamental concept upon which the therapeutic experiment to be described is based. Axiomatically, allergic disease exemplified by hay fever and asthma is known to occur most frequently in patients with an hereditary predisposition to these diseases. In the family histories of 480 allergic children where the histories of the

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diseases occurring in consanguineous relations could be obtained in satisfactory detail, asthma and hay fever were discovered in antecedents, in the brothers and sisters of antecedents, or in siblings in 92 per cent of the families. Eighty-nine of these families with two or more children served as small units for an epidemiologic study of the transmission of colds. In respect to upper respiratory infection and concomitant allergic diseases the children in these families fell into three categories: normal children; children with recurrent upper respiratory infections without allergic manifestations caused by food, pollens, or inhalant antigens; and a group with asthma and hay fever who had multiple sensitivities both clinically and by skin tests. Some children with frequent winter infections were included in this group because they were skin-sensitive or later developed asthma and hay fever. The normal children, aside from tonsillitis and occasional infections of the nonrespiratory type, had few respiratory infections which could not be ascribed to contact with other members of the families or with children with epidemic colds. Although the children in the other groups had epidemic colds, some also had recurrent respiratory infections which were not in the course of epidemics and were not transmitted to normal close contacts. These recurrent respiratory episodes were characterized by fever, purulent rhinitis, and bronchitis or asthma. The ensuing cough persisted for two or three weeks. Reinfections occurred at intervals of four to six weeks. As a result, these patients were seldom free of some upper respiratory disturbance. The ratio of colds in these children to those among the normal children was about four to one. It is believed that these repeated infections were caused by bacteria harbored in the upper respiratory tract and occasionally, since a few almost parallel infections were observed among allergic members of a family, to contact. But these infections were never epidemic in a family so presumably were not initiated by a highly contagious cold virus or virulent bacterium. Although bacteria are considered the etiologic agents, the possibility that certain strains of viruses might cause such reinfections in chronic carriers must remain an open question until tests for cold viruses less laborious than the present transmission experiments are available. The children in the second group, those subject to reinfection but showing no manifest allergies, were apparently potentially allergic, an assumption based on the allergic antecedent history, on the similarity of the infectional pattern to that of frankly allergic children, and the observations that some of them followed for several years developed hay fever in adolescence.

RATIONALE OF THERAPY

The results of treatment with filtrates of upper respiratory pathogens in a number of asthmatic children with an infectional pattern resembling that of the potentially allergic children described in the preceding paragraph, were published in 1939.[15] These asthmatic children were given a mixture of filtered, four-day broth cultures of the common upper respira-

tory pathogens during successive winters. Most were distinctly benefited. Bacterial filtrates were used because patients with streptococcal or staphylococcal infectional edema not improved by vaccines were helped by the administration of filtrates of streptococci or staphylococci. A mixture of filtrates was necessary because the floras in cultures of the upper respiratory tract in successive attacks of asthma were variable and unpredictable.

Chronic infectional edema[11] is a circumscribed inflammatory edema of the face or extremities following recurrent attacks of erysipelas or localized staphylococcal infection. After gross foci of infection had been treated, inoculations with filtrates of four-day cultures of *Streptococcus hemolyticus* or *Micrococcus pyogenes* var. *aureus* checked the erysipelas or staphylococcal infections after treatment with bacterial vaccines proved ineffective. These filtrates contained toxins, freed nucleoprotein still active on skin test, and bacterial polysaccharides. According to growth curves of the cultures calculated from counts of visible living and dead bacteria, 1 ml of a four-day filtrate was usually equivalent to about twenty billion bacteria. The areas involved by these inflammatory edemas were highly sensitized to streptococci or staphylococci. When infections with these bacteria occurred in parts of the body other than the inflamed face or extremity, or overdoses of filtrate were given subcutaneously, focal reactions occurred. The possibility of establishing a similar immune mechanism in asthmatic patients seemed reasonable, but the infectional pattern in asthmatics was much more complicated inasmuch as the bacterial flora of the respiratory tract changed in successive attacks of infectional asthma.

Cultures of the sputum and nasopharynx made after the initial phase of recurrent asthmatic attacks showed extremely variable floras. Potential pathogens appeared and disappeared in successive attacks in an unpredictable manner. If there were gross foci of infection, the bacteria inhabiting these foci appeared in recurrent attacks; otherwise the appearance of potential pathogens seemed to be a reflection of the flora found at large in the population as determined at the time from miscellaneous cultures. An increase in pathogens occurred in the late winter months. The results of cutaneus tests with refined nucleoproteins[12,13,14] of the microörganisms, repeated at intervals of several weeks over a period of two or three years, were as variable and unpredictable as the floras of the cultures. Obviously cultures made in the fall months were not representative of the bacteria found in the late winter floras. For this reason a basic mixture of filtrates of *Micrococcus pyogenes* var. *aureus,* hemolytic streptococci, *Diplococcus pneumoniae* type II, *Streptococcus viridans* and *Micrococcus catarrhalis,* the bacteria most commonly found in the late winter cultures, was prepared; and substitutions and additions were made for the individual patient according to the cultures obtained after the first cold in the fall months.

The stock strains were pure smooth or mucoid, and the toxins, with the toxin-producing bacteria, were of almost constant level in cultures grown

under similar conditions. Thirty-eight children in the group with recurrent colds without manifest allergies were treated with filtrates prepared in a similar manner.

CLINICAL DATA

The children were brought in for study because it was believed that they were allergic, or because previous treatment had failed, or because the children were unable to attend school or kindergarten, or because the recurrent infections had undermined their general health. In families with asthmatic children or parents, there was fear that these children also might develop asthma. The majority (twenty-seven of thirty-eight children) were first seen in the spring or fall months of the third year of recurrent infections. Twenty-eight had previously had tonsillectomies, four simple adenoidectomies, and seventeen had been given some variety, either stock or autogenous, of catarrhal vaccine. There were eleven who had had otitis media, two pneumonia, two measles, and one pertussis. Many had started kindergarten but were withdrawn because of poor attendance. Some, however, attended irregularly. A few were of school age. Six of the children in whom treatment was not begun the first year because the parents considered the course too exacting were brought in the following year. While a few of the children were robust, twenty-two were underweight, pale and wan, and had poor appetites. The gain in health experienced during the summer when they were well was lost after three or four colds in the late fall months.

Reasonably accurate records regarding the onset, the course during treatment, and the subsequent results have been obtained. The onset was not abrupt. Nocturnal nasal occlusion and purulent discharge were observed when some of the children were two years of age. These symptoms increased in severity in succeeding winters, upper respiratory infections became more frequent and severe, and bronchitis with nocturnal cough was more stubborn and persistent. Coarse rales were found in some attacks. In these respects the course was similar to that of children who develop asthma following a series of respiratory infections. However, few of these children had had measles, whooping cough, or pneumonia, and failed to show positive reactions when tested with pollens and common inhalant allergens. The low incidence of cutaneous reactions to these allergens, as compared to the high incidence of positive reactions among most children who have asthma following colds, and the fact that so few had had pneumonia, measles, or whooping cough—diseases which frequently initiate the asthmatic state in children with this predisposition—may have been determining factors as to whether or not these children would be asthmatic. Four of these children, while under treatment, had severe bronchitis with respiratory distress. The attacks were not repeated and were not reported as asthma. All have been followed beyond the eighth year of age. Since, according to our data, the initial asthmatic attack oc-

curred before the eighth year in 85 per cent, and before the sixth year in approximately 70 per cent in 340 children with asthma under the age of twelve, the probability that any of these children will become asthmatic before adolescence is not great.

Inoculations were begun in October or early November after cultures were made following the first cold. *Hemophilus influenzae* filtrate was added to seven filtrate mixtures one year, that of Friedlaender's bacillus was added to two mixtures, nine filtrates were fortified with the filtrate of a pneumococcus that was found predominately in fall cultures, and a filtrate of *Micrococcus pyogenes* var. *aureus* was either substituted or added twenty times. *Hemolytic streptococci* were found in only four cultures made in September, October, and early November. Cultures made later, in February and March, showed an increase in the prevalence of potential pathogens, but the filtrates were not modified at this time even though influenza bacilli were found in many cultures late in the winter in certain years. Undiluted filtrate mixtures and dilutions of 1:10 and 1:100 were employed. A preliminary inoculation of 0.1 ml of the 1:100 dilution was given to children who had not received filtrates previously. There have been no reactions to this dose. Two-tenths, 0.5 and 0.8 ml were then given on successive weeks. Four children had fever and nasal congestion following intermediate doses of this dilution. It was difficult to establish tolerance in these children. Subsequently, 0.2, 0.4, 0.6 and 0.8 ml of the 1:10 dilution, and then doses of the undiluted filtrate increasing from 0.1 ml to 1.0 ml by increments of 0.1 ml were given weekly. The sites of injection occasionally became markedly swollen as the doses were increased, but tolerance could always be established by reducing the dose, then increasing the amounts given in successive inoculations more carefully. These local reactions, which appeared within a few hours, were painful, and often lasted two or three days. Some reactions were accompanied by fever and cough the following day, evidence that the resipratory tract was sensitized to some of the bacterial products in the filtrate mixture. When 1.0 ml of the undiluted filtrate could be tolerated, inoculations were given at two- or three-week intervals until the late spring months. Reinfections seemed to occur when the intervals between inoculations were too long. No inoculations were given during the summer, a season when these patients normally had few respiratory disturbances. Continuance of treatment in successive years depended on the results of therapy the previous year. Reactions were rare after the first year of filtrate therapy.

RESULT OF THERAPY

The parents were asked to keep notations regarding the number of respiratory infections with fever between September and June of each year. Other data collected regarding days of confinement to the house and the severity of the cough following each infection seemed unreliable because

of the extreme variations in criteria. Very satisfactory data for twenty children were submitted. During the winter previous to the one in which treatment with filtrates was begun, these twenty children required medical attention for 136 respiratory infections with fever. During the first year of inoculations severe infections were reduced to sixty-one and during the second to twenty-three of moderate severity. Five of the twenty were given inoculations the third year. During this third winter the respiratory infections were largely epidemic, resembling ordinary colds in symptomatology and duration. The results in these twenty children appear representative of the group of thirty-eight. In this larger group there were four failures. After the second year these four children were taken to Arizona, where they improved. After inoculations were begun, two to two and a half months were required before decided improvement was noticeable. Then the colds became less severe and shorter, and occurred at longer intervals. Weight and appetite improved. After a series of inoculations the epidemic colds in these children were often shorter and less severe than those in the presumably normal children in the family. The nasal mucous membranes, which were pale and edematous between attacks, assumed a normal appearance when the recurrent infections had been controlled.

DISCUSSION

Unfortunately the circumstances under which these patients were studied did not permit the accumulation of a series of untreated patients for control. As far as treatment is concerned, the clinical experiment has certain controls within itself. When treatment with filtrates was begun, improvement was noted after several weeks of therapy. The first and second years during which inoculations were given are to be compared with the year previous to treatment. These years show marked improvement. There are two objections which may be raised. One is that normal children may have a series of colds when they first start school or kindergarten; the second is that if these children were allergic, as is assumed, they might outgrow their allergies. But careful observation of normal children, and of supposedly normal children in allergic families, showed that their series of colds occurred early in the fall, seldom continued past the mid-year holidays, and were usually epidemic. The children that were treated showed an entirely different infectional pattern. Their infections continued until summer, were usually not epidemic, and showed no indication of being milder in the two or three years following the onset. Regarding the observation that children outgrow their allergies, Flensborg[4] found that 60 per cent of children with asthma were still asthmatic in early adult life although the attacks had become milder and were farther apart. The children which he treated might be compared with the series of children which he studied, although admittedly the allergic disease in our series was not as severe a manifestation of allergy.

The mode of action of the filtrates is hypothetical. The filtrates used in the treatment of infectional edema contained toxins. Even though the patients with recurrent erysipelas had sufficient circulating antitoxin to prevent a scarlatiniform rash and only an occasional patient with staphylococcal infection reacted cutaneously to staphylococcal toxin, it was thought that the recurrences of infection might be controlled if the antitoxin levels could be elevated. Estimations of the levels at intervals showed such irregularities even after infections were checked that the amount of circulating antitoxin evidently had little to do with the therapeutic results. On the other hand, acquisition of tolerance to filtrates has been outstanding. This tolerance has been local, focal, and general. Many patients had swollen arms, some had respiratory reactions, and a few had fever during the course of inoculations. All these reactions could be overcome by reducing the doses given and approaching the reactive point of dosage carefully. More than one effort was sometimes necessary before adequate doses could be given. Whether this tolerance was the result of hyposensitization or of immunization has not been determined. Many possibilities must be considered, especially in allergic patients. Intracutaneous tests with solutions of nucleoproteins obtained from the bacteria with which the basic filtrates were prepared, gave diminished or negative reactions in children in the spring after their series of inoculations when compared to the strongly positive reactions obtained the previous November or December with the nucleoproteins to which they were then sensitive. A standard intracutaneous dose (0.1 ml of solution containing 1 mg N in 100 ml of nucleoprotein prepared according to methods used previously[12,13]) was used for testing. This observation suggests that the acquired tolerance to the filtrates and resistance toward winter colds may have resulted in part from an immunity to bacterial nucleoproteins—a complex of nucleoprotein and somatic polysaccharide—and to nucleoprotein fractions in the filtrates. The results of this therapy suggest immunization rather than hyposensitization because the effects have been relatively permanent in contradistinction to the effects of hyposensitization, which seem more temporary.

Colds and reinfections similar to these described in children have been observed in adults who responded to the same treatment. But accurate study of the epidemiology of the infections in adults was impossible because of the mutlitude of contacts and the varying environments. The families described with their several manifestations of allergy were the most satisfactory units for observation and have been used only to exemplify the ramifications of a much broader problem.

CONCLUSIONS

Children, considered potentially allergic, have numerous respiratory infections which are apparently not initiated by viruses but are recurrences of bacterial infection. Usually these infections appear intrinsic. These

recurrent infections are not confined to children but may occur in adults and are most common in allergic people. Continued inoculations with filtrates of cultures of upper respiratory pathogens control these infections. Mixtures of filtrates have been used for the inoculations, because the floras in cultures during recurrent infections have been unpredictable, none of the potential pathogens having been pre-eminently predominant in successive infections.

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COLD URTICARIA

Investigations Concerning Its Pathogenesis

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IN an earlier report dealing with a very sensitive case of cold urticaria, we[23] expressed our opinion that this case belonged in the category of true physical allergy, in spite of a negative passive transfer, because it fulfilled all the other requirements of allergic hypersensitiveness. We suggested that there might be cases presenting the same clinical picture where the reagins are bound more strongly to the cells so that they cannot be demonstrated in the circulating blood with the usual methods.

Since then we have observed and studied four additional cases of cold urticaria. These investigations may allow us a better interpretation of the phenomena of cold urticaria and generally of physical allergy.

REPORT OF CASES

Case 1.—J. C., a woman, aged thirty-one, for five to six years used to have wheals due to cold water or cold wind both in summer and in winter. The wheals would appear all over the body, but only on the parts exposed to the cold. The mucous membranes were not sensitive. There were no general symptoms. Her allergic personal and family history was negative. She did not suffer from hemoglobinuria. The basal metabolic rate was + 26 per cent. No focal infection was present; the Wassermann test was negative.

On June 21, 1948, a test was performed on the forearm by contact with flowing water of 18° C for one to one and one-half minutes upon the forearm. The test resulted in the appearance of disseminated smaller and greater wheals surrounded by hyperemic flares and followed by intense itching. A three-minute application of the cold water resulted in confluence of the wheals; the whole forearm became edematous. There was no distant reaction on the arm such as a lymphangitis. Mechanical insult caused a moderately marked, non-itching dermographism. The differential blood count was normal, eosinophilia 3 per cent. The patient reacted normally to histamine and a little stronger to acetylcholine.

Case 2.—F. D., a woman, aged thirty-seven, for five to six weeks had developed swelling and itching urticarial wheals on those parts of her body which were exposed to cold wind or water. Mucous membranes were also hypersensitive: the oral mucosa swelled when ice or cold water were applied. She had no general symptoms. During the last weeks she had lost considerable weight. Allergic family and personal history was negative. No hemoglobinuria was present. Her menopause had started six months ago. No focus of infection could be found. The Wassermann reaction was negative.

A test performed by letting water of 18° C flow upon the forearm for two to three minutes resulted in the appearance of disseminated, severely itching wheals. The half to one-minute application of ice did not provoke wheals. A two- to three-minute exposure to ice resulted, however, in a few wheals upon the slightly edema-

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tous skin; later she did not react at all to ice. There was no distant reaction, nor any general symptoms. A strongly marked dermographism was present, followed by an itching edema, which even increased when exposed to cold. The blood count was normal, eosinophilia was 6 per cent. Her reactivity to histamine and acetylcholine was normal.

Case 3.—B. K., a woman, aged forty-four, for one to one- and one-half years had reacted to cold water or wind with an urticarial rash on the parts exposed to cold. The mucous membranes were also hypersensitive. There were no general symptoms. She had previously suffered from dermatitis, and once she had had an urticaria due to gastritis. She suffered from anacidity. She had suffered from diabetes since 1947. Sugar in the urine was 4.2 per cent, in the blood 250 mg per cent. At the time of the test the blood sugar level was normal due to insulin treatment. She had no focal infection. The Wassermann test was negative. There was no hemoglobinuria. Her family history was negative.

Tests made by contact of flowing water of 18°C upon the forearm for three minutes were followed by a strong hyperemia and smaller or larger itching urticarial patches partially confluent. There was no lymphangitis, no general symptoms, and no dermographism. The blood count was normal, eosinophilia 4 per cent. Reactivity to histamine and acetylcholine was normal.

Case 4.—K. G., a man, aged thirty-seven, in 1945 worked strenuously as a prisoner of war at a temperature of 35° C below zero. In November, 1947, he had an attack of malaria. In May, 1948, he observed the appearance of urticarial wheals due to cold water or wind. Stronger cold effects, e.g., a cold bath, caused general symptoms also: headache, vertigo, tachycardia, anxiety, and feeling of impending death. The attack usually lasted a few minutes only. He did not observe any hemoglobinuria. Family and personal history were negative. The Wassermann test was negative.

On August 22, 1948, a test was performed by letting water of 18° C flow upon the forearm for three minutes. He showed smaller or larger itching urticarial patches surrounded by hyperemia, but only upon the site of exposure. There was no distant reaction. Cold did not produce any general symptoms if applied upon a limited surface only. He showed no dermographism. Blood count: slight anemia, eosinophilia of 2 per cent. Normal reaction to histamine and acetylcholine.

EXPERIMENTAL INVESTIGATIONS

Determination of Threshold Values.—This was carried out in two directions:

(a) To determine the lowest and highest temperature to produce wheals.

The lowest temperature could not be determined because we did not apply anything colder than the ethylchloride spray. The upper limit went up to 26-30° C.

1. J.C.: chlorethyl—ice—water (26°C)
2. F.D.: chlorethyl—ice—water (28°C)
3. B.K.: chlorethyl—ice—water (26°C)
4. K.G.: chlorethyl—ice—water (30°C)

(b) To determine the minimal time of exposure needed to produce wheals at various temperatures given.

This threshold value was generally short, but it depended upon the

TABLE I. THRESHOLD VALUES IN COLD URTICARIA

	Chlorethyl Spray	Ice	Water 6°	10°	18°	26°	30°C
1. J.Cs. 1948. VI.	2″	2″	5″	15″	30″	1′	0
1948. X.*	4″	—	—	—	1′	—	0
2. F.D.	0	0	1′	—	2′	—	0
3. B.K.	10″	15″	1′	—	3′	—	0
4. K.G. 1948. VIII.	—	4″†	—	—	1′	3′	—
1949. I.	—	10″	—	2′	3′	3′	3′

*After administration of niacin tablets.
†On sunburnt patients the threshold value increased 5-8 times.

TABLE II. HEMOCLASIC CRISIS FOLLOWING EXPOSURE TO COLD

Case	Temperature		Tension		Pulse		Leukocyte count		Refraction*		Sedim.† rate		Eliciting Cold Effect
	b	a	b	a	b	a	b	a	b	a	b	a	
1. J.Cs.**	37.2	36.1	120/80	110/90	88	76	8200	7700	13481	13477	—	—	Forearms, water of 18°C, 10 minutes
2. F.D.	36.9	36.5	120/90	105/80	96	82	5300	5100	13500	13495	5/10	17/28	Arms, chest, water of 18°C, 5 min.
3. B.K.	37.3	36.3	140/90	125/90	100	100	7700	6600	13500	13495	16/40	20/40	Forearms, water of 18°C, 10 min.
4. K.G.	36.4	36.1	130/80	120/80	75	68	6900	6200	13509	13500	—	—	Forearms, water of 18°C, 3 min.
5. F.R.	37.4	36.8	140/90	120/80	86	96	6800	5200	—	—	6/17	8/19	Left forearm, water of 9°C, 5 min.
	37.2	36.6	140/80	120/75	90	80	7300	5700	—	—	9/24	10/24	Forearms, water of 9°C., 10 min.

b—Before.
a—After.
*Determined with Abbe's refractometer.
**In cases 1 and 5 the venous blood had a vivid red color taken after exposure.
†Sedimentation rate 1 and 2 hours.

applied temperature too. In our cases it increased parallel with the rise of the temperature.

Cold exposures above the threshold value caused an extensive edema of exposed surfaces in Cases 1, 3, 4, and partially confluent wheals in Case 2. During these examinations patient in Case 4 had two typical attacks of malaria; following this he did not notice any cold urticaria for a few days. Ice and water of 18° C produced only a normal reaction without itching. However, the blood still contained reagins at this time, and passive transfers were successful. Consequently the phenomenon did not correspond to the "antianaphylactic state." After four to five days the hypersensitivity to cold returned gradually; on the fifth day the threshold value to ice was still two minutes instead of four seconds as previously.

In all the four cases we provoked a *hemoclastic crisis* by a stronger, respectively longer exposure to cold. A more or less marked crisis occurred in all cases accompanied by a diminishing of body temperature with a maximum decrease of 1.1° C. In the following Table II one can also find the dates of an already published case[1] (F.R.) who reacted with strong general symptoms. All determinations have been carried out *before* and *after* the crisis.

EXPERIMENTS WITH PASSIVE TRANSFER

Although F. R. showed severe general symptoms, a well-marked hemoclasic crisis, lymphangitis, and distant reaction, the passive transfer with the Prausnitz-Küstner method failed. However, it was successful in the four new cases. One must be very careful in claiming the failure of a passive transfer test and can do so only if the reaction gives a negative result on many test persons and with different methods. Not all persons are appropriate recipients. For example, it happened in the case of J. C. that the first transfer to three test persons failed completely. Later it was revealed accidentally that the transfer of the same serum, staying in the refrigerator for more than a month, led to faultless positive reactions in other test persons. The serum of F. D. transferred to seven test persons gave positive results in two cases only. The sera of F. D. and K. G. could be easily transferred to appropriate test persons with a positive result. The transfer of the serum of J. C. showed lesser results but generally succeeded. The serum of B. K. needed special technical artifices for achieving success. We have used both cold water (to 18° C) and ice as provoking stimuli. In the case of F. D. the ice was ineffective when applied to the skin, but in the passive transfer experiment it produced the same urticarial reaction as cold water. Much depends, also, upon the time of exposure. In the case of J. C. the reaction could be obtained only when ice was applied for at least three minutes. The Prausnitz-Küstner (P-K) test was not influenced by storing the serum at room temperature, in an incubator, or in a refrigerator, although one might suppose that the cold reagins would diminish in a serum kept in an icebox.

The combination of cold urticaria and urticaria factitia occurs rather often (Abramson,[1] Liebner,[15] Kenedy,[9] et cetera). In our case F. D. a true mechanical allergy was also present, because we could demonstrate not only cold reagins but also "mechanical" reagins in the serum of the patient. These reagins could be tested not only *simultaneously*, but also *following* each other; i.e., after the P-K reaction provoked by a mechanical stimulus regressed, a specific, immediate urticarial response could be obtained by applying cold.

The failure of the passive transfer may prove a complete lack or a low level of reagins in the blood, which cannot be demonstrated by the routine technique. This explanation is supported by those cases in which the usual P-K reaction fails but reagin can be detected by aid of certain artifices. Among these we mention first our old method which consists in taking the blood *after* the application of the allergen (Lehner and Rajka[13]). It has been shown that the serum contains more reagin and gives a more intensive P-K reaction if taken after than before the exposure to cold (reagin-increasing method). This has been demonstrated often in cold urticaria (Lehner,[11] Liebner,[16] Weissenbach and Brisset,[26] Pernyes-Pietsch,[20] Lehner, Rajka and Barkan);[14] it has occurred

even that the transfer succeeded only with a serum taken after exposure (Affolter[2]). There are also examples among other physical urticarias which prove this observation (e.g., in a case of urticaria solaris of Beal[3] the passive transfer could be carried out only with serum taken *after* exposure to light). We could also observe this phenomenon in our present cases. Furthermore, when the passive transfer was elicited several times at the same site, we observed the following:

The first P-K test showed a positive reaction with both sera, but when the test was elicited again, the site of the first serum (taken *before* exposure) did not react, while the site of the second one (taken *after* exposure) still developed a wheal. This fact also suggests that the serum taken after exposure contains more reagins than the other (Table III).

TABLE III

Serum K.G.	Elicitation[1]	Elicitation[2]
I.	17-20*	minim.
II.	17-21	10-12
Control serum	0	0

I—Serum taken before exposure to cold.
II—Serum taken after exposure to cold.
*Diameter of wheals in mm.

REVERSED PASSIVE TRANSFER

We also performed the P-K test in cold urticaria on a skin surface previously cooled with ice. The usual P-K test was negative in the case of B. K., and it did not succeed until the patient's serum had been injected into the skin of a recipient whose skin had previously been exposed to ice; it was hoped that the minimal free reagin would be better bound to the cells of the skin. Our method is based upon the reversed passive transfer. The technique is as follows: the patient's serum and the normal controls are injected into sites previously cooled with ice for three to four minutes; the injections are repeated five to ten minutes later. Immediately after application of ice the temperature of the skin decreased 18 to 21° C and at the moment of the second injection 6 to 10° C. The reversed passive transfer always failed in our cases, although we used sera which contained P-K reagins and tested persons who had previously shown a positive response. We wished to decide whether the cold reagin had been exhausted in the reversed P-K test, and therefore after twenty-four hours we applied ice to the passively sensitized sites. By this method we could evoke wheals even in Case 3, where the usual P-K test failed to demonstrate reagin (Table IV).

One may suggest also that we were dealing here with a *delayed resorption* or, rather, fixation of reagins. Therefore we have carried out parallel experiments with sera containing adrenaline. A mixture of 0.9 ml serum and 0.1 ml Adreneol* (in 1:1,000 dilution) was used, and by this method

we actually could perform a passive transfer in the case of B. K. (Table IV, Case 3).

TABLE IV

Serum	Skin Sites Cooled with Ice	Mixture of Adreneol and Serum	Usual Prausnitz-Kustner Reaction
1. J.Cs.	9-11*	11-14	9-10
2. F.D.	13-15	15-16	12-15
3. B.K.	9-10!	11-12!	0
Control	0	0	0

Elicited by 3 minutes' application of ice after 24 hours.
*Diameter of wheals in mm.

The adrenaline mixture method proved itself valuable when the usual P-K test gave negative or minimal results, due to a low reagin level (e.g., in old sera). Thus the J. C. serum kept for thirty-four days produced a minimal reaction on one of the recipients, while on the site of the Adreneol-serum mixture a marked wheal formation took place. The fixative effect of vasoconstriction due to cold is also supported by the observation that vasodilatation shortens the absorption of reagins; this is shown by the *lack* of delayed reaction in cases where wheal formation has been accompanied by strong hyperemia and edema (Seeberg[24]).

We have tried to determine the supposed higher reagin content of sera taken *after* exposure to cold by the aid of a *dilution* test. In the case of F. D. the sera taken before and after exposure gave equally positive reactions up to a dilution of 1:20. The only difference was that the wheal from the serum taken after exposure seemed larger and harder. Naturally the size of the wheals diminished with serial dilutions, and with repeated elicitations the sites of higher dilutions were exhausted first (Table V).

F. D. July 12, 1948. Blood (No. I) was withdrawn. The patient then washed his arms, chest and back with water of 18° C for 10 minutes, and then the second blood sample was taken (No. II). Serial dilutions of both sera and of the control serum were injected into two recipients S. and B. (0.1 ml intracutaneously). Forty-eight hours later the reaction was elicited by a three-minute application of ice.

NEUTRALIZATION TEST

As mentioned before, sera kept in the refrigerator reacted as well in P-K testing as those stored at room temperature. Even some sera kept in a frozen state for a few days contained an almost unchanged quantity of reagin. The only difference consisted in the diminished size of the wheals where frozen sera were used. Thus the *in vitro* neu-

*Adreneol is adrenaline in which action is prolonged by means of mucic acid and bisulfurosum.

TABLE V

1948		Provocation	Concentrated	Dil. 1:10	Dil. 1:20	Dil. 1:40
July 14						
Recipient S.	F.D.I.		16-18*	11-12	10-10	min.
	F.D.II.		20-23	12-14	11-12	min.
	Control	1	0	0	0	0
Recipient B.	I.		11-12	11-12	min.	0
	II.		12-13	12-14	min.	min.
	Control		0	0	0	0
July 15						
S.	I.		16-22	12-15	9-12	0
	II.		18-24	12-15	10-13	0
	Control	2	0	0	0	0
B.	I.		13-14	follicular	0	—
	II.		14-15	edema	0	—
	Control		0	0	0	—
July 16						
S.	I.		15-18	flat wheal of un-		0
	II.		17-20	determined borders		0
	Control	3	0	0	0	0
B.	I.		11-13 flat	min.	0	—
	II.		12-13 flat	min.	0	—
	Control		0	0	0	—
July 19						
S.	I.		12-14	9:12 flat min.		0
	II.		12-19	not measurable min.		0
	Control	4	0	0	0	0
B.	I.		min.	0	0	—
	II.		min.	0	—	—
	Control		0	0	—	—
July 20						
S.	I.		flat, not	0	—	—
	II.		measurable	0	—	—
	Control	5	0	0	—	—
B.	I.		min.	0	—	—
	II.		min.	0	—	—
	Control		0	0	—	—

*Diameter of wheals in mm.

tralization failed. The *in vivo* neutralization occurred in the same way. The site of the reaction was not exhausted; further positive reactions were provoked by stronger cold stimuli (contact of ice lasting three, five, ten minutes) at the passively sensitized site. A positive P-K reaction was elicited three to four times following repeated application of cold at intervals of twenty-four and forty-eight hours. Furthermore, the second elicitation resulted usually in stronger wheal formation than the first one. This might be due to the known nonspecific biological fluctuation (first an increasing then a decreasing response after repeated physical or chemical stimulation of the same area); it has also been observed with other allergens (Lehner and Rajka[12]). It also occurred that a patient with a minimal reaction at the first stimulation developed a well-marked positive response after the second provocation test. This phenomenon is illustrated by the following experiment (Table VI):

The sera of F. D., J. C., and B. K. were injected into the thighs of two recipients (T. and S.) (0.1 ml i. c.). The skin of the recipients had been previously cooled with ice for three minutes. The sera of F. D. and J. C. gave positive results on these two recipients in a former experiment, but the passive transfer of serum of B. K. failed. Serum

TABLE VI

	Provocation 1	Provocation 2	Provocation 3	Provocation 4
Recipient T.:				
F.D. serum—I.	12-16*	15-22!	9-11	follicular
A II.	14-15	14-17	10 11	edema
I.	10-12	15-17!	8-10	edema
B II.	11-13	15-20!	8-11	edema
Control	0	0	0	0
Recipient S.:				
F.D. serum—I.	12-15	15-17!	idem	min.
II.	14-16	17-18!	but	min.
J.Cs. serum	12-13	13-14	flat-	min.
B.K. serum	flatedema	12-13!	ter	0
Control	0	0	0	0

I—Serum taken **before** exposure to cold.
II—Serum taken **after** exposure to cold.
*Diameter of wheals in mm.

"A" was injected five minutes after the recipient's skin was cooled, and serum "B" ten minutes later. There was no immediate reaction; the reverse P-K test was negative. After twenty-four, forty-eight, seventy-two, ninety-six hours we were able to elicit the reaction by an application of ice for three minutes.

A Prausnitz-Küstner reaction can be repeatedly elicited under normal conditions also. On the average, three provocations succeeded. However, on a previously cooled skin site, at least four reactions could be elicited. This fact shows that the reagin content of a previously cooled skin site remained on a higher level. A P-K reaction may be also repeatedly elicited on skin sites passively sensitized with serum-Adreneol mixture. A slight neutralization could be demonstrated only in case of a transfer of a *frozen* serum; in this case the provocation of a positive reaction succeeded but once or twice.

Consequently, the cold reagin is just as resistant against cold and conservation as other reagins. Sera kept for sixty and ninety days, respectively, in the refrigerator still gave positive P-K tests. But like other reagins the cold reagins are also thermolabile: the serum reagin loses its activity when kept at a temperature of 60° C during an hour.

When the synthetic antihistamines were discovered, the problem of specific desensitization seemed to lose its importance. As also claimed by Gaddum,[7] antihistamines have an especially good effect in cold urticaria. Osborne, Jordon and Rausch[19] reported excellent results in cold urticaria by administration of Pyribenzamine. The drug is effective also for prevention. Fifty mg Pyribenzamine given before exposure to cold prevented the urticarial eruption (Kesten[10]). Perry and Horton[21] reported good results with Pyribenzamine, Kallos[8] with Antistine, Feinberg and Friedlaender,[6] McElin and Horton,[17] Notier and Roth[18] with Benadryl. Chmel and Hegyi[5] could not provoke cold urticaria after the intake of Neo-Antergan. Skin infiltrated with Phenergan did not react to cold. There are some reports about failures too, but we can confirm the following based on our own observations:

1. The synthetic antihistamines particularly relieve the pruritus.
2. They mitigate the severity and duration of the urticarial rash.
3. They increase the threshold value of cold urticaria.
4. They mitigate or prevent the P-K reaction in cold urticaria.

However, the administration of adrenaline and to some extent also of ephedrine may produce similar results. The effect of antihistamines is more definite and prolonged.

As mentioned before, the antihistamines interfered also with the P-K reaction (Vallery-Radot, Mauric and Halpern[25]). In the case of F. D. where we could demonstrate cold reagins, as well as the "mechanical" ones, the P-K reaction became negative to cold and was also remarkably diminished to mechanical stimuli after a week's administration of Pyribenzamine in doses of 50 mg three to four times daily.

On the basis of the experiments, we gave antihistamines to the patients, chiefly Pyribenzamine, for a few weeks. The result was satisfactory; they did not develop wheals or pruritus even on cold or rainy days.

PATHOGENESIS OF PHYSICAL ALLERGY

It is still not decided whether the physical stimulus liberates first a *secondary allergen* in the organism which reacts with the reagin, a theory supported by the majority of authors, or whether the physical agent itself, in our instance the cold, *activates directly* the reagin, as some enzyme (Rajka[22]). The failure of the reversed passive transfer experiments speaks in the first line against the formation of secondary allergens. When we applied the cold stimulus first, and injected the serum containing the reagins afterwards, the reaction failed. However, we might expect an immediate urticarial rash due to the union of the secondary allergen formed by the cold effect and of the reagin present in the patient's serum, just as if a previously present reagin unites itself later with the secondary allergen.

Of course, further experiments are necessary to settle this question. The most important one is the failure of the distant provocation in passive transfer tests. When we injected serum containing reagins into the upper arm of appropriate recipients in semicircular shape, and immersed the forearm in cold water, or applied ice the next day, we could not obtain a positive urticarial reaction in any case; however, the application of cold directly to the sites of the serum injections resulted in an immediate reaction. Thus the negative experiments speak at least against the existence of a diffusible secondary allergen. The supporters of the theory of a secondary allergen may assume that the allergen is not diffusible, and therefore, it cannot provoke a distant reaction. Naturally there is a more simple explanation too, namely, that no secondary allergen exists at all and no distant elicitation can take place.

From theoretical considerations one may expect that the blood flowing

from the cooled forearm should act as a cold allergen due to its lower temperature and thus it should provoke reactions on the sites of the previously administered serum, containing the reagins. But this did not occur, with the exception of one case. We do not know as yet the mechanism of this phenomenon; perhaps we cannot cool the circulating blood enough. It is certain that all our four cases of cold urticaria were strictly localized and we could never elicit distant reactions in the course of the exposures to cold. On the other hand, the already published case of F. R. (Rajka and Asboth[23]) developed hyperemic stripes on the arm, leading towards the axilla and also some wheals over the stripes, as in Bray's case;[4] some wheals appeared even on other distant sites too and all this occurred after cooling the forearm. Unfortunately, in this case the P-K reaction could not be elicited and consequently there was not any possibility of eliciting a distant P-K reaction.

The aforementioned exception was one of the recipients. We have injected the patient's serum into his *back,* previously cooled with ice, and the next day he developed typical reactions on these sites after cooling his *forearm* with ice or cold water. Repeated experiments gave the same result, but it failed on other persons. This single experiment naturally does not allow any important conclusions.

We must conclude, therefore, that the question of the secondary allergen in physical allergy cannot be decided with the present experiments, though most experiments seem to give evidence against it.

SUMMARY

1. Four cases of cold urticaria are reported. There were no, or only slight, general symptoms; we found a more or less pronounced hemoclastic crisis and a positive Prausnitz-Küstner reaction in all cases.

2. In one of the cases the cold urticaria was associated with true allergic urticaria factitia with transferable reagins.

3. If the reagin level of the blood is low, various methods can be used:

(a) *Reagin-increasing method:* the serum taken after exposure contains more reagin.

(b) *Reagin-fixation method:* if the patient's serum is injected into a skin site previously cooled with ice, the reaction gives positive results even in those cases where the usual Prausnitz-Küstner test had failed. The theory of reagin fixation, and of retarded reagin absorption, respectively, is supported also by similar experiments with the administration of vasoconstrictors (adrenaline, et cetera.)

4. The *quantitative* Prausnitz-Küstner test gave positive reactions up to serum dilution of 1:30.

5. The Prausnitz-Küstner test could be elicited repeatedly on the same site (the second provocation gave the strongest urticarial reaction) even with sera kept in an ice box, or with frozen sera. Thus neutralization

could be achieved neither *in vivo* nor *in vitro*. The cold reagin is very resistant to cold: it may be conserved a long time, but it is thermolabile.

6. Synthetic antihistamines relieve the pruritus approximately for two hours and mitigate or prevent the wheal formation for an hour. They increase the threshold value of manifest urticaria and prevent the Prausnitz-Küstner reaction.

7. The failure of the reversed passive transfer and the lack of distant elicitation of passive transfer reactions give evidence against the existence of a secondary allergen in physical allergy.

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ACTH AND CORTISONE

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PSYCHOTHERAPY IN MULTIPLE SCLEROSIS

Part IV

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AMONG research workers in the field of multiple sclerosis through the last decade there has been a growing acceptance of the idea that allergy plays a major role in the etiology of this disease.[1,2,4,5,6,10,11,12,16,18,19,20,21,24,25] During the past five years we have examined and treated on a private patient basis 1511 individuals suffering from this condition. These have been treated with histamine,[3,8,9] curare,[15,23] physical therapy, but—above all—psychotherapy.[14,22] Pyschotherapy, we feel, plays the major role in all of our various approaches to the symptomatic treatment of these patients.

To understand the major role of psychotherapy in multiple sclerosis, one must understand the pathology in the acute and subacute cases. This pathology can be considered analogous to urticarial wheals, scattered throughout the entire central nervous system at various times. The skin and the central nervous system originate from the same embryological layer; namely, the ectoderm. Because of this, it is reasonable to assume that the entire central nervous system might be susceptible to the same allergic insults as the skin. It is well known to all of us as allergists that urticaria results from emotional and food allergy insults. When the urticarial wheals occur on the skin or along the intestinal tract, there is no serious damage, as there is no pressure exerted. However, in a bony cavity such as the skull or vertebral column there is small room for expansion. Therefore, through pressure, the blood supply to certain areas is obliterated; and if this pressure continues long enough, the destruction of tissue in these areas occurs with resulting scar tissue or sclerotic plaques. If the urticarial wheals disappear and the pressure is removed soon enough, the symptoms which have resulted from pressure disappear. A remission results.

It is well known that the majority of multiple sclerosis patients exhibit signs of emotional instability. We are of the opinion that most have neuroses. This resolves itself into the chicken-or-the-egg proposition. Does the neurosis occur first, or do the symptoms of multiple sclerosis come first? That is a question very difficult to answer, as it is hard to state definitely where subjective symptoms of multiple sclerosis begin

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and neurosis stops. But, after carefully analyzing our cases we believe that any allergic insult (including emotional) can trigger the initial attack. There is no doubt that a great many patients have their first exacerbation as the result of an emotional trauma following accidents,[7] fright, worry, or even great joy, just as urticaria will occur on the skin as the result of any of these.

Emotional onsets and exacerbations are exemplified by a few of our following cases, among many:

During a battle in the South Pacific in the last war, an engineering officer on a cruiser was caught between decks and sealed in. When freed several hours later, he was paralyzed from the waist down. A short time thereafter a remission occurred, followed later by exacerbations and typical multiple sclerosis.

A priest going to the altar to be ordained suffered paralysis of his foot resulting in his stumbling. This continued with the usual development of the condition.

While prisoners of war were undergoing indignities on marches or in prison camps in Japan and Germany, several had the beginning symptoms which later service-connected their multiple sclerosis.

Others have felt the coming parasthesias and numbing while attending funerals of friends or making funeral arrangements for relatives.

Not a few first noticed symptoms of the disease during divorce proceedings or immediately following.

One girl became paralyzed on the day before her wedding.

The effects of pregnancy[13,17] in triggering the disease or its exacerbations have long been recognized. Ordinarily mixed causes can be claimed here. But certainly only the emotional factor was involved in one of our cases who first took to a wheel chair and then had to be hospitalized as a bed patient when his wife was going through her last days of pregnancy.

In treatment these conditions should be gone into thoroughly and rationally with the patients, explaining to them the degree to which their emotional upsets influenced the course of their disease.

When the pattern of urticarial whealing within the central nervous system is established in the individual, recurrences may be brought about by many other allergic insults besides the original one.

It is recognized that multiple sclerotics are usually dependent individuals, even before their disease has shown itself. When the diagnosis is made and they learn for the first time the facts about the condition from which they are suffering, they usually become very much perturbed. At this point they are looking for some one whom they have confidence in to guide them. This is the physician's opportunity. But commonly they are informed in a kindly but firm manner that nothing can be done for them—that they have a hopeless, incurable disease—that it will progress

from a limp to a cane, to crutches, to a wheel chair, and then to bed. With this added emotional trauma they usually have a very severe exacerbation, and many go to bed and remain there for the rest of their lives. Others struggle along with this treatment and that treatment, frequently administered by irregular practitioners.

It has long been recognized that the majority of multiple sclerosis cases improve under any and all types of treatment at first, but later usually have an exacerbation and stop that particular type of treatment. The reason for this improvement, in our opinion, is that relief of emotional strain through something being done reduces the degree of the urticarial pressure within the central nervous system. However, when their symptoms do not entirely disappear, they become emotionally upset and have another exacerbation. If these patients can be taken in hand before demyelination has progressed too far and can be given a psychological crutch by their physicians, this relapse usually will not occur.

The psychotherapy should be both supportive and constructive. The patients should be shown by statistics that nearly half of them will continue to be able to work regardless of whether they have treatment or not, that if they only keep working and walking, with treatment most of them can stay on the job; also, that very, very few patients die of either multiple sclerosis or its complications. It is not the killer usually pictured; neither is it necessarily the hopeless crippler. They should also be assured that with proper exercise muscle tone can be retained and nearly all contractures prevented, especially if they are faithful to treatment.

Euphoria is supposed to be characteristic of multiple sclerosis. This we have not found to be true. Only about 10 per cent of our 1511 have had this mood. At least an equal number suffered from the severest types of depression. The others varied between these extremes. A great many that might appear to be in a euphoric condition exhibit this merely as a defensive mechanism to cover up their inner feeling of tension regarding the general attitude of other people toward them and their fear of the future. They have a tendency to be overtalkative, co-operative and amiable towards their physician, hoping that he will do everything he can to help them out of their dilemma. If the physician treats them coldly, rejects them, and assumes a hopeless attitude towards their future, they retire within themselves, their spirits dropping to a low point. This, of course, is an emotional trauma of the worst sort. In our clinic, we make every effort to meet patients more than half way in friendliness and co-operation, using this so-called euphoric attitude as one of our best vehicles in psychotherapy.

Multiple sclerotics are almost always normal individuals physically in their dreams. During these times they walk, dance, work, and perform all tasks as entirely normal individuals and seldom as crippled, deformed, or sick people. Some have told us that they are happiest when they

can sleep and dream. This can easily be understood, considering their condition when awake.

Allergy management lends itself remarkably well to psychotherapy, as most of the exacerbations can be traced to allergic insults from physical, food, miscellaneous, or emotional allergic episodes. When this is called to patients' attention, they are relieved of their anxiety and this robs the disease of much of its fearfulness and uncertainty as to the future.

Physical therapy and curare are very useful in relieving the residuals of former exacerbations by controlling spasticities and improving muscular action. This also puts the patient at ease with reference to their disabilities, helps build morale, and reduces their anxiety state. These procedures lend themselves to supportive psychotherapy. By these means patients are kept from becoming discouraged; they look to their physician with confidence, believing he will guide them around future pitfalls. This relieves fear of the future, which in turn reduces anxiety and increases self-reliance.

CONCLUSIONS

Psychotherapy, in our opinion, is the most valuable procedure we have in the handling of multiple sclerosis patients. For best results other forms of treatment must be used as vehicles to support this therapy. Considering the pathology in the acute and subacute conditions, our approach in treatment from a psychological standpoint, as allergists, must be in a degree the same as we would use in approaching treatment in cases of angioneurotic edema and acute or chronic urticaria. In allergy management all emotional factors must be evaluated. But, above all, defeatism and ideas of hopelessness in these cases must be cast aside, with every effort being made to increase morale and stimulate hope.

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DISCUSSION

CHAIRMAN HAROLD A. ABRAMSON, New York, New York: I feel that Dr. Jonez is doing more for disseminated sclerosis than anyone else in the world. He has the largest group of patients and he is spending a great deal of time with them, recording in a scientific way as much data as can be made available. But there is a more important point that I think should be emphasized. Dr. Fremont-Smith pointed out this afternoon that people who are ill become frightened people, and when they seek medical advice, it is important that the physician is not frightened because of his inability to cope adequately with the disease. Certainly, disseminated sclerosis is one disease with which we cannot cope adequately today. I am glad to say that Dr. Jonez is not a frightened doctor and that he has had the courage, in the face of a great deal of criticism, to expand and develop facilities and theories of therapy against a good deal of opposition. There is no doubt that his method of approach, utilizing the various disciplines—pharmacologic therapy, immunologic therapy, and psychologic therapy, is a good example of the best in the practice of medicine, and I do hope that he will be able to give us more information next year.

There is one important point that I should like to emphasize in connection with the more technical aspects of Dr. Jonez' paper that has to do with the therapy of the patient with disseminated sclerosis as well as with the patient having any chronic illness. In recent discussions, I have learned that one of the first feelings to be repressed in the patient is the feeling of hostility in the presence of a chronic disabling illness. This hostility must be repressed because of the extreme dependence that the patient has on relatives and friends. The patient therefore is placed at once in a conflict situation in which hostility and dependence are suddenly and forcibly intermixed. The problem of facing this conflict is not a simple one. I believe that it is very important that the individual treating this

illness make it clear to the patient that he has mixed feelings on these points and recognize the consequences in dealing with the difficult life situations engendered by the nature of the disabling forces.

DR. WILLIAM KAUFMAN, Bridgeport, Connecticut: Dr. Jonez deserves much credit for his courageous, dynamic approach to the management of patients with multiple sclerosis through every modality of treatment which offers the patient hope of some degree of subjective or objective benefit.

In my own studies, I have learned that in order to help a patient with multiple sclerosis to make the best possible adjustment to his chronic illness, it is necessary early in the course of treatment to give attention to the emotional problems of his family. The family of a patient with multiple sclerosis have a difficult life situation, and unconsciously they develop much repressed anger and rage at the chronically sick individual who is a constant problem in social adjustment and a constant drain of economic as well as emotional resources.

Relatives of patients with multiple sclerosis have told me of their terror dreams which follow a fairly consistent pattern and indicate the direction of their subconscious thinking: The person wakes with terror, having dreamed he killed the patient by pushing him down a flight of stairs. Sometimes the relative reports panic upon awakening, but for a time cannot recall the dream itself. When he remembers the dream he is horrified, and guilt-stricken, and may have for a few days a transient, clinically obvious acute anxiety state; more often he has chronic anxiety and fear without an apparent object. The dream is merely an extension of his unconscious death wish, which he suppresses during the daytime when he notes the clumsy ambulation of the afflicted person, who might actually die from a spontaneous accidental fall downstairs, thus freeing the family from current problems. For example, the husband of one of my patients lived in constant "fear" that he might get a call at his office telling him his wife had fallen down the stairs and broken her neck.

The murderous dream and the daytime "fears" of close relatives of the patient with multiple sclerosis are so vivid and real that these people overcompensate by being oversolicitous about the patient's welfare, overprotecting him at every turn, and in effect forcing him to take a more dependent role than he would otherwise do. As a result, psychotherapy of the patient becomes extremely difficult because of his family's highly conventionalized, socially acceptable solicitude for the patient (which is meant defensively to neutralize their hostile impulses toward the patient).

By supportive, corrective, and reconstructive psychotherapy, it is possible to drain off the relative's suppressed rage and hostility toward the sick person, thus lessening his guilt about having destructive feelings, and his fear lest his unconscious wish might be fulfilled. Thus, the relative can learn to be more objective in his attitudes toward himself and toward the sick person. (It is undesirable in the process of readjustment to permit the patient's family to develop punitive overcompensation by neglecting the patient and doing nothing to help him.)

The sick patient should be encouraged by his family and physician to become as independent as his chronic illness permits him to be. Social and emotional adjustments in the family circle can be improved, and the patient in particular benefits because there is less overt and covert suggestion from others that he is a helpless invalid.

DR. M. G. MEYER, Michigan City, Indiana: The basic pathology of this illness is such that I find it, personally, very hard to reconcile myself to the belief that a disturbance of mental composure can account for it.

On the other hand, reasonably good clinical and laboratory evidence exists that

the pathology can be reproduced by allergen-antigen reaction. There is no doubt that an attainment of mental composure is desirable in these patients. Davison and many others here have shown that the reactive ability of the individual from an allergic standpoint is greatly altered by the psychogenic equilibrium or non-equilibrium of the patient from week to week or even hour to hour. It seems to me, then, that we must take this latter concept into full consideration rather than accept a psychosomatic etiology as a complete explanation.

A multiple sclerosis patient of mine volunteers the information to me without questioning that she can produce nystagmus, vertigo, and an increase in the spasticity of the residual spasticity in her left limb by ingesting eggs. I have seen her do this repeatedly, yet she has almost a compulsive obsession to eat eggs at eight to ten week intervals. Is it then easier to treat her by insistence that she eliminate eggs from her diet, or is it necessary to delve into her psychiatric background to find out why she has this obsession for eggs?

DR. R. J. BRENNAN, Champaign, Illinois: Two years ago at our Fifth Annual Congress in Chicago, I had the pleasure of discussing Dr. Jonez' paper "Histamine Therapy in Multiple Sclerosis." Today he has presented another important phase in his therapy of this disease. His present treatment consists of allergic management, histamine, d-Tubocurarine, physiotherapy, and psychotherapy. The most important of these is psychotherapy, as Dr. Jonez has brought out so clearly in his paper of today.

Last year Dr. Jonez reported on a new method of administering histamine in a repository menstruum. He had found by the Van Slyke method of volumetric blood oxygen level determinations that histamine when given in large enough doses raises the oxygen content of venous blood to the arterial level. When histamine is given intravenously, the venous blood remains at arterial level for less than an hour. Histamine when given by iontophoresis raises the oxygen level of venous blood to the arterial level and maintains it there for from two to three hours. However, when given in a repository menstruum, the oxygen of the venous blood is retained at an arterial level for between twenty-four and forty-eight hours.

Dr. Jonez and myself during the last year have used this repository preparation with beneficial results in chronic atopic eczema, dermatitis, asthma, and hay fever, as well as in many cases of multiple sclerosis.

I should like to ask Dr. Jonez whether he believes that repository histamine will duplicate the therapeutic achievements of ACTH and cortisone. Considering the low cost of repository histamine as compared with either ACTH or cortisone, it is rather startling when we think of what might be done with histamine in this form.

DR. JONEZ: In reply to Dr. Brennan's question, while it is not directly pertinent to the subject of my paper today, the question is a very interesting one in light of some of our observations. We have given respository histamine* to 412 different patients. A large number of these, of course, are sufferers from multiple sclerosis; however, it has been given to many patients suffering from various diseases of allergy. Some of our results have been very dramatic, the action of this drug resembling to a marked degree many of the reported results from the use of ACTH and cortisone, so much so, that we have come to the conclusion that histamine in some manner brings about a production of both ACTH and cortisone by the body itself. I hope to report further and in more detail on this subject to the College next year.

*Histamine diphosphate suspension in oil and wax supplied through the courtesy of Endo Products, Inc.

SOME PSYCHOLOGICAL ASPECTS OF THE TREATMENT OF PATIENTS WHO HAVE FOOD ALLERGIES

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AN UNTOWARD reaction to the ingestion of a wholesome food can be caused by a psychogenic mechanism as well as an allergic one, or by a combined psychogenic and allergic mechanism. While it is difficult to evaluate the relative importance of psychogenic and allergic factors in the untoward reactions of a given patient, sometimes it is of considerable clinical importance to do so in treating a patient.[5,11,15,16]

Many factors may be responsible indirectly for allergenic and psychogenic idiosyncratic reactions to foods. First of all, there are important cultural determinants of attitudes toward food and toward eating. For example, in this country eating is commonly regarded as a necessary but pleasurable activity; among the Balinese eating is regarded as a disgusting procedure, and infants are taught to react to food as children here are taught to react to excrement.[14] In various religions, the eating of certain food or food combinations is forbidden. Thus, orthodox Moslems and Jews may have an aversion to eating pork, Hindus to eating beef, and the inadvertent ingestion of a forbidden food can cause in such people severe psychosomatic reactions, usually consisting of nausea and vomiting and anxiety.

In many parts of the world, the eating of human flesh has been regarded as a delicious treat.[4] Today the moral and ethical codes prevailing in our culture forbid the eating of human flesh, although the killing of human beings is still culturally acceptable in time of war. A veteran of World War II told me that in campaigning in the South Pacific when he was literally starving, he could not bring himself to eat monkey meat because monkeys were "too much like people." In this country, household pets are often regarded as members of the family, and the conventional taboo against eating the flesh of these pets is symbolically an extension of the taboo against cannibalism in general.

Superstition in the past has attributed to certain foods desirable or undesirable properties: e.g., oysters were supposed to improve sexuality, and tomatoes (love apples) were considered poisonous. Certain creatures (insects, rodents, snakes, eels) are regarded by many as filthy, disgusting and unsuitable for eating, even though the flesh is tasty and nutritious. Often severe psychosomatic reactions occur when an individual who has eaten a wholesome food of this type learns the nature of the material he has ingested. A patient of mine who visited Mexico told me how

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much she enjoyed a certain crisp and delicious pretzel-like food. When by chance she learned that these morsels were actually fried caterpillars (gusanos del maguey), she became very ill indeed.

Even sophisticated physicians have been known to develop strong aversions to certain organ foods; a cardiologist I know became ill as soon as he learned that a savory stew he was enjoying was made of beef heart. A pathologist had a similar reaction when he realized he was eating a liver and kidney pie. Both physicians, however, could eat beef tenderloin without discernible adverse psychosomatic reactions—and, indeed, with the greatest enjoyment.

Food likes and dislikes may be a reflection of national, regional, or local eating habits. Familiar foods are usually relished when prepared in familiar ways, and offer a type of emotional security to us simply because they are familiar. Foods prepared in unfamiliar ways are often regarded with distaste and suspicion; if we find it difficult to make adjustments generally, we do not want to have to make adjustments to new foods.[1]

An infant early learns to appreciate that certain foods, particularly milk, allay hunger and give comfort. As the baby grows, he becomes better able to distinguish differences in texture, temperature, and taste of foods. He learns to accept certain food properties as desirable, and reject others as undesirable. He learns also that he can influence parental attitudes by his acceptance or rejection of foods.[8] If he refuses food he may get extra parental attention in the form of bribery, coaxing or punishment; if he eats "seconds" he may have rewards, praise, extra maternal love and affection.

For each individual, foods very early in life become associated symbolically with diverse emotional meanings, so that for any given individual there is scarcely a food which can be considered to be emotionally neutral. In American life such foods as chocolate, hot dogs, candy, and ice cream have come to be reward foods. Parental insistence that such foods as spinach, carrots, and milk must be eaten by a child often calls forth resistance on the part of the child, which is retained even in adulthood as a symbolic rejection of parental authority. On the other hand, forbidden foods usually have a great appeal for the child, particularly when he is told he can have coffee, tea, beer, et cetera, only when he is "grown-up." Sometimes overindulgence in these foods in later adult life is overdetermined by the individual's desire to make up for earlier deprivations of childhood and to assert his adultness.[3,9]

The child learns to imitate his elders in both the acceptance and rejection of food. A submissive child is one who is "good" and eats everything offered; a naughty child is one who refuses food offered. The child as he grows into adulthood has developed conditioned eating habits so that he tends to eat the same foods prepared in the same way, over and over again. People are often allergic to their favorite foods, probably because

they have eaten these foods frequently and in large amounts. Sometimes people dislike foods to which they are allergic, even when they don't know about their allergies, and avoid these foods without quite knowing why.[7,12,13]

Psychogenic reactions to food may take many psychological forms: anxiety, guilt, depression, hostility, passive dependent attitudes, euphoria, relaxation. The most common somatization is to the gastrointestinal tract, and this is clinically manifest through nausea and vomiting, epigastric discomfort or pain, intestinal cramps, aerophagia, belching, and rarely diarrhea. Symbolically in these ways the gastrointestinal tract rejects the offending food from the body.[3,9]

An individual usually avoids those foods to which he has psychogenic reactions of nausea and vomiting. Uusually before he can eat these foods without experiencing untoward psychosomatic reactions, such a patient must be reconditioned emotionally through psychotherapy. For example, a patient of mine was served what he thought to be chicken pie at a family dinner. He said it was delicious, and asked for a second helping. Several hours later his wife told him with some amusement that he had eaten not chicken, but rabbit pie. Immediately he became ill. He retched and vomited, became weak, had muscle tremors, and hypotension. When I saw him he looked as if he were going into shock. Subsequently I learned that as a child he had had rabbits as pets, and regarded them as though they were siblings. Thus, the eating of rabbit meat seemed to him to be the equivalent of cannibalism. He recovered gradually from his illness, but not until he was reassured by his wife that she would never again serve him rabbit as food. For a long time he would not even eat chicken unless he could identify it at the table as such.

Another man had violent arguments with his aged mother, whom he saw about once a week. Sometimes following his weekly visit he developed severe hives, although at other times he did not. Analysis of his food-symptom diary showed that when he ate egg-containing food and quarrelled with his mother, he had a severe attack of hives; when he did not eat egg, he could quarrel with his mother without having hives. When he ate egg and did *not* see his mother, he did *not* develop hives. This man did *not* develop hives unless he experienced a particular emotional state within a few hours of eating egg-containing food. When he was able to change his attitude toward his mother, he could see her, eat eggs, and not have hives.

It is in such instances that psychotherapy seems to be successful in preventing allergic manifestations (in this case, hives). However, the elimination of egg from this man's diet also prevented the appearance of hives. Thus, the allergist and psychiatrist can arrive at the same therapeutic end-point (prevention of hives) by using different methods of influencing the patient's homeostasis.

Changes in mentation may result from the ingestion of allergenic foods

as a direct result of what seems to be a cerebral allergy.[2,7,12,13] However, reactions which simulate cerebral allergy may arise directly from emotional conditioning to a food. For example, one of my patients, following the ingestion of fresh cherries, invariably had a severe reaction, including irritability, depression, and definite suicidal thoughts, lasting as long as four days.

However, this man could eat stewed or canned cherries without any untoward reaction. Finally he was able to tell me about the most humilitating experience of his life: when he was nine years old he had climbed a neighbor's cherry tree and stolen cherries. The neighbor caught him and gave him a beating. The boy ran home and told his father about the beating, thinking to get sympathy, but instead the father also gave him a beating and a lecture on the virtues of honesty.

After this patient was able to understand the psychodynamics of his reaction, he has been able to eat fresh cherries without any untoward reaction whatever. This reaction to fresh cherries represented a primary psychogenic reaction to wholesome food which simulates the allergenic mental syndrome; obviously, this psychogenic reaction could also have been prevented by removal of fresh cherries from the patient's diet.

Primary allergenic food reactions are always followed by secondary psychogenic reactions which may prove to be more incapacitating than the initiating noxious stimulus.[6,9] We should realize that any person who experiences even a single severe allergic reaction (e.g., angioneurotic edema) is not the same person he was before this reaction; for some time thereafter he is usually fearful, apprehensive, afraid of a recurrence; and his total behavior is modified, not only in relation to foods but also to life situations.

A patient who develops a steady state of allergic reactions resulting from daily ingestion of an allergenic food, such as wheat, is often just as uncomfortable on one day as the next. It is not unusual to find that such an individual has made a reasonably good adjustment to his illness and his life problems, although he operates at an over-all reduction in efficiency because of his allergic illness.[7]

But often an individual who has unpredictable intermittent allergic food reactions such as headache, fatigue, and mental syndromes, develops severe frustration reactions since he can never predict when he will be sick and when he will be well. He may develop non-problem-solving behavior[10] and become intensely concerned with minutiae, often neglecting to do necessary work. This type of obsessive compulsive behavior in response to unpredictable and recurrent ill health is often seen in allergic patients. Through psychotherapy, one can remove the secondary reaction patterns, permitting the patient to develop problem-solving behavior with expansion of the total field of interest. With exclusion of the offending food, one can remove the primary allergenic reaction and often the secondary psychogenic reaction patterns.

Every physician treating patients who have food allergies should attempt to become acquainted with the makeup of his patient, including the emotional significance of various food materials to the patient. The physician must be prepared, in addition to giving the patient expert allergic care, to give him competent psychotherapy so that the patient will be able to make good physical and emotional adjustments and the occurrence of idiosyncratic food reactions will be minimized.

SUMMARY AND CONCLUSIONS

Untoward reactions to the ingestion of wholesome foods may be caused by psychongenic or allergic mechanisms, or combinations of the two. Sometimes it is important to evaluate the role that psychogenic and allergic factors play in untoward reactions of a patient.

Food becomes associated symbolically with diverse emotional meanings very early in life, so that for each individual scarcely a food is emotionally neutral. Psychogenic food reactions may include anxiety, guilt, depression, hostility, passive dependent attitudes, euphoria, relaxation. The most common somatization of psychological reactions to food is to the gastrointestinal tract, including nausea and vomiting, epigastric discomfort or pain, intestinal cramps, aerophagia, belching, and rarely diarrhea, all being part of the riddance reaction.

Primary allergenic food reactions are followed by secondary psychogenic reactions which may be more incapacitating than the initiating noxious stimulus. A person with a steady state of allergic reaction resulting from daily ingestion of offending foods may make reasonably good adjustments to his illness and life problems, although his over-all efficiency is lowered by his allergic illness. But often an individual with unpredictable intermittent allergic food reactions such as headache, fatigue, and mental syndromes develops severe frustration reactions, since he can never predict how he will feel. He develops non-problem-solving behavior and becomes intensely concerned with minutiae in an obsessive compulsive manner, and often neglects to do necessary goal-directed work.

Psychotherapy can help patients to overcome incapacitating secondary conditioned-behavior patterns. Elimination of allergenic foods removes the etiologic agent, thereby relieving the patient of primary allergenic and secondary psychogenic reaction patterns. Combined allergic therapy and psychotherapy usually yield the best results.

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HYPOALLERGIC PENICILLIN III.

Histadyl-Penicillin

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IN TWO earlier papers[15,16] a new method of reducing the number of reactions to penicillin by the addition of an antihistaminic drug (Decapryn®) to the diluent was introduced. The present report continues this work using another antihistaminic agent (Histadyl®).

The use of the antihistaminic drugs continues to be somewhat empirical, and in treating patients with these drugs it is frequently necessary to vary the dosage and the intervals between medication; often it is essential to try several different antihistamines before arriving at the best one for the particular condition being treated in a certain patient. As yet we have found no ideal antihistaminic drug which would lead us to discard all others. Structural formulas and animal experiments give us leads but frequently are not borne out by clinical experience. To discover the best available antihistamine to prevent penicillin reactions requires much material, many patients, and considerable time for observation. Arbitrarily, an eight months' period of use was decided upon.

In the earlier series, the hospital patients were divided into two groups. The patients in one group, being the controls, received aqueous potassium penicillin G in normal saline. The patients in the other group received the same penicillin in the same concentration (units per ml), the only difference being the addition of the antihistaminic agent to the saline diluent.

While controls fill a necessary place in any experiment, if the control rate of reaction is too high or too low, the average observer is accustomed to discard the data. Also, if no controls are used, double the number of patients can be placed on the new combination during the same period of time. In other words, it is felt that what is desired is some means of lowering penicillin reactions to an insignificant level, far below any of the reported reaction rates, rather than adding another reaction rate and demonstrating that the antihistamine had lowered it so many per cent as demonstrated in the first series.

In the previous papers on penicillin blood levels, fast absorption vs. slow absorption and regular penicillin vs. procaine penicillin were discussed in detail. The references appear in the bibliography.

Patients in the hospital are apparently better managed on aqueous crys-

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Histadyl (thenylpyramine hydrochloride) was supplied through the courtesy of Eli Lilly and Co., Indianapolis.

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talline penicillin, as blood levels and side reactions can be controlled much more easily. It is also felt that in an experiment of this type the results are more obvious. For office or home treatment crystalline penicillin in sesame oil with 2 per cent aluminum monostearate added is preferred. Therapeutic penicillin blood levels are maintained for twenty-four hours, and here again there is a control of level and side reactions not possible with higher dosage, slowly absorbed procaine penicillin. Although few cases of procaine sensitivity have been reported, they are not rare.

METHOD

The Histadyl-Penicillin used was prepared by the following method: Histadyl® was available in sterile 10 gm ampules. One of these was dissolved in each 1000 ml of sterile buffered saline and used as diluent for the crystalline potassium penicillin G (Squibb or Pfizer). Therefore, each ml contained 100,000 units of penicillin and 10 mg of Histadyl® (Histadyl —1.0 per cent).

During the eight months of these studies, 1,312 patients received over 10,000,000,000 units of Histadyl-Penicillin. The individual dose varied from 100,000 to 300,000 units given from one dose only to one dose every twenty-four, twelve, eight, six, four, or three hours. The lowest total dose given any one patient was 100,000 units and the highest 48,600,000 units. The average dose for all patients was 9,000,000+ units. Approximately half of the patients had been previously given penicillin in some form.

RESULTS

Any type of reaction, local or generalized, which could be attributed to penicillin or any other drug was referred to the author, who personally examined it. Only six reactions were so reported and are briefly summarized:

Case 1.—J. P. had received penicillin two years previously for two months. He was first given aureomycin, which produced a stomatitis. Histadyl-Penicillin was substituted—200,000 units being given twice daily for ten days. At this time the patient developed a mild urticaria, which subsided in one day with cessation of the penicillin treatment and the administration of an antihistaminic agent by mouth.

Case 2.—E. R. had prevously been given a long course of penicillin and developed a severe urticarial reaction. After two injections of 300,000 units each of Histadyl-Penicillin an inguinal rash developed. He was changed to a type of antihistamine-penicillin in oil; the rash cleared, and this medication was continued as long as needed without further reaction.

Case 3.—R. M., after receiving 300,000 units of Histadyl-Penicillin twice daily for ten days, developed a generalized macular pruritic rash and low grade fever. As penicillin was needed no longer, it was stopped and the reaction completely cleared in five days, during which time the patient took an oral antihistaminic drug.

Case 4.—O. N., suffering from third degree burns, was given Histadyl-Penicillin, 200,000 units twice daily for seven days and four times daily for two days. At

this time a generalized erythema developed, which cleared in five days after penicillin was stopped and an oral antihistaminic drug was administered.

Case 5.—A. S., seventy-eight years old and moribund, received 200,000 units of Histadyl-Penicillin twice daily for five days. Furacin® was also applied locally to a large ulcer in the perianal area. A morbilliform rash appeared on the back and buttocks and became rapidly generalized. He expired a few days later—the rash still present although all drugs had been stopped.

Case 6.—M. S. received procaine penicillin on seven successive days before entering Brown General Hospital for the treatment of his gonorrheal arthritis. He received 300,000 units of Histadyl-Penicillin three times daily for four days more, at which time a mild urticarial eruption appeared. Penicillin was stopped and oral anthistamines given, clearing the reaction in twenty-four hours. Histadyl-Penicillin was then started again but increased to 500,000 units every three hours. The mild urticaria reappeared but was never sufficient to stop medication, which was given six more days.

Even though all six of these cases are considered reactions due to Histadyl-Penicillin (and Cases 5 and 6 are highly questionable) the reaction rate is 0.45 per cent.

All patients noted the local anesthetic effect of the Histadyl.® Even though as much as 5 ml was given at one injection, there were no complaints of pain or residual tenderness. None of the side reactions of oral antihistamines, such as drowsiness, dizziness, headache, or gastrointestinal upsets, occurred at any time.

Therapeutic results were as good as with any other type of penicillin. Frequent blood counts, other laboratory studies, and urinalyses showed no adverse reactions due to the added Histadyl.

DISCUSSION

The reaction rate using Histadyl-Penicillin in a large series of patients (0.45 per cent) was far below that obtained using another antihistamine previously (2.4 per cent). This may possibly have been due to using this antihistaminic drug in 1 per cent solution instead of 0.5 per cent as was done in the earlier work.

The amount of antihistamine contained in the oil solution with 2 per cent aluminum monostearate is 1.5 per cent of oil-soluble base, but there are 300,000 units of penicillin per 1 ml. With this solution reaction rates have been negligible.

One must agree with Cannon et al[5] in saying, "For the treatment of diseases in which initial high peaks are desirable, it might be advisable to use crystalline penicillin G in aqueous solution, as this is most quickly absorbed and excreted, or combinations of this preparation with newer delayed absorption products that are now available." However, it seems fitting to add that if an antihistamine in proper concentration accompanies the penicillin, the injection will be practically painless and the reaction rate materially reduced.

SUMMARY

Further studies using a different antihistamine (Histadyl®) in the diluent of crystalline potassium penicillin G are presented. In all, 1,312 patients were treated with this Histadyl-Penicillin. Six reactions developed, two of which probably were not due to the Histadyl-Penicillin. Although these are included, the reaction rate is 0.45 per cent when 1 per cent Histadyl® is added to the diluent for the penicillin.

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A COMPARISON OF ANAMNESTIC AND PERENNIAL THERAPY IN THE MANAGEMENT OF ALLERGIC RESPIRATORY DISEASE

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OVER the years we have noted that patients with allergic respiratory disease who had previously been well treated were significantly protected during a pollen season with only a few preseasonal injections. The protection was good even if the antigen was administered only a week prior to the appearance of atmospheric pollen. The patients we treated just prior to the season were treated rapidly, and the initial dosage was higher than if begun in the January-April period. Strangely enough, our incidence of constitutional reactions was not increased by this rapid immunization.

Von Pirquet[1] recognized that when anaphylactic hypersensitivity is once established, it will gradually wane if there is no further contact with the antigen; but if the antigen is then reintroduced, the hypersensitivity state will reappear in a decidedly shorter time than was required at first. Bacterial hypersensitiveness is also rapidly returned to a high level by fresh contact of the tissues with the specific bacteria. This is called the anamnestic (recollection) reaction. This term is also applied to renewed production of antibodies following contact with related antigens.

Loveless[4] studied the anamnestic response principle in a series of patients who had been well treated previously, following which they were allowed a rest period of 200 to 300 days. Her study was concerned primarily with thermostable antibody production. She reported that once an immunological ceiling was reached in "booster" therapy, increased doses would not raise the titer. The average maximum dose for maximum response in her cases was 6750 units. Doses of 20,000 units did not increase such response. It was noted that after a thorough primary course of injection therapy, one secondary stimulus was as effective as another, provided the preceding titers and rest periods were comparable. The secondary titers were more favorable when a large dosage was attained in the primary series. The anamnestic responses appeared to be influenced by the size of the primary course. Furthermore, intensive primary therapy seemed to extend its favorable influence against the first season.

Clinically, we noted that patients who had been well treated over a long period of time prior to their subsequent breakdown seemed to respond better to anamnestic therapy. It was also felt that previously untreated patients who presented themselves for treatment during a ragweed season and who voluntarily discontinued a short time after therapy was begun did not respond well to anamnestic therapy. Strangely enough, in our ex-

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perience their response to continuous perennial therapy subsequently was, on the whole, not gratifying. Our clinical results seemed to correlate Loveless' studies of titer.

TABLE I. A COMPARISON OF ANAMNESTIC AND PERENNIAL RAGWEED THERAPY

Result	Perennial 88	Anamnestic 85
Excellent	32	27
Good	33	43
Fair	20	11
Poor	3	4
Systemic Reaction	2	2

We are not prepared to submit any statistical evidence at this time to substantiate this hypothesis. We have felt so strongly on this question that we have discouraged patients from starting therapy unless we could follow through over an extended period of time. Because of this policy, we have accordingly not had sufficient experience with anamnestic treatment following purely preseasonal therapy.

In the fall of 1949 we discontinued treatment on a number of our pollen disease patients who had received at least one year of primary therapy. We made tentative dates for their anamnestic treatment. The grass pollen patients were asked to report by May 1, 1950. Many returned between May 1 and May 6. Some reported a week early because of circumstances.

Our date for starting ragweed therapy was after July 15. If practical, we tried to begin August 1. However, since this is the period of vacations, we allowed sufficient leeway for this factor. To all ragweed or timothy sensitive patients whose maximum primary dosage was 12,500 Cooke units, we gave an initial dose of 500 units and then doubled the dose every third or fourth day if there was no residual swelling. We were interested in getting a maximum end-dose of 2,500 to 4,000 P.N. units. The average number of injections was six. The last injection was administered just prior to the appearance of atmospheric pollen. The dosage scale in all cases depended on the amount received in the primary therapy. Patients who had received less than 12,500 units as a maximum dose initially received proportionately reduced doses.

The standards used for evaluation of clinical results were as follows:

1. Excellent—Patients who had no untoward symptoms during the pollen season and accordingly required no palliative relief.
2. Good—Individuals who had mild symptoms, requiring palliative relief during a period not to exceed one week.
3. Fair—Patients who showed definite improvement over untreated seasons in both subjective and objective symptoms, yet who required medication over a period longer than one week but not longer than three weeks.
4. Unimproved—Those patients who required medication longer than three weeks and subjectively felt no better than in untreated seasons.

For comparative purposes, a study was made of the results obtained in a similar group of patients who were being treated perennially and who had received a minimum of twelve months of therapy. No patients were included in this group whose type of therapy might be called preseasonal or who were known to have a clinically important psychogenic overlay.[2]

The perennial ragweed cases considered for this study numbered eighty-eight. Of these, thirty-two were classified as having no appreciable symptoms during the ragweed season of 1950. Thirty-three were classified as good. Twenty cases were considered fair. There were three unimproved patients in the group.

A total of eighty-five case histories of patients treated anamnestically, using the "booster principle," were studied. Of these, twenty-seven had excellent results, forty-three were classified as good, 11 as fair. There were four patients who said they were unimproved over their original state prior to any therapy.

Further analysis showed that eighty-two per cent of the anamnestically treated patients were either excellent or good from our classification standpoint. This compares favorably with 74 per cent of our perennial cases who had entirely satisfactory results. Because there are many factors involved in hay fever, we tried to ascertain the over-all picture by comparing these patients in 1950 with their previous seasons, when they were treated perennially. Forty-nine remained in the same classification as in previous years. Twenty-two were better under anamnestic management and were therefore classified in a more satisfactory category. Fourteen were not as well as during their perennial management, and had to be counted in a less satisfactory group. With these figures in mind, we feel that we can say that about eighty-five per cent of the patients treated anamnestically were as well or better than during perennial management. In the remaining group it was felt that only four had regressed to the point where therapy was not beneficial. This figure compares favorably with the three failures in the perennial group. We were unable to explain the reason for the lack of success in these cases, since we did not treat any patients who had not been benefited by previous perennial therapy. In our anamnestic ragweed group of eighty-five patients, forty patients were being treated because of the recurrence of symptoms.

We also treated thirty-six patients anamnestically with timothy extract, using sixty-two perennially treated patients as controls. Of the thirty-six in the anamnestic group ten reported excellent results. Nineteen were good and seven fair. About 80 per cent of the patients responded satisfactorily: that is, of either excellent or good. In the perennial group of sixty-two, nineteen were excellent, and twenty-nine were good, with eleven fair and three unimproved. There were forty-eight patients in whom the results were either excellent or good.

When the 1950 anamnestic results were compared with previous perennial results, we found that seventeen patients remained in the same classi-

fication as when treated perennially, and seventeen were placed in a more satisfactory category, with two who regressed and were placed in a less satisfactory group. In this group of thirty-six patients, sixteen were being treated because of the recurrence of symptoms.

TABLE II. A COMPARISON OF ANAMNESTIC AND PERENNIAL TIMOTHY THERAPY—1950

Result	Perennial 62	Anamnestic 36
Excellent	19	10
Good	29	19
Fair	11	7
Poor	3	0
Systemic Reaction	2	1

TABLE III. AN EVALUATION OF ANAMNESTIC THERAPY WITH PREVIOUS PERENNIAL THERAPY IN THE SAME INDIVIDUALS

Result	Ragweed 85	Grass 36
Same	49	17
Better	22	17
Worse	14	2

In our experience, the incidence of systemic reactions with rapid booster therapy was no greater than in standard perennial therapy, provided the patient had been previously well treated. In this series, there were two systemic reactions in the ragweed perennial group of eighty-eight and two in the ragweed anamnestic group of eighty-five. There were ten patients in this latter group who had experienced constitutional reactions during their period of perennial therapy. We incurred two systemic reactions in the timothy perennial group of sixty-two and one on the timothy anamnestic group of thirty-six. In this group, there were six patients who had constitutional reactions during primary therapy. On these patients, the original anamnestic dosage dilution was at least ten multiples lower than the maximum dilution attained in the primary course.

SUMMARY AND CONCLUSIONS

1. The results in patients previously well treated with ragweed or timothy antigen compared favorably with the control groups of patients receiving perennial therapy. When the results of "booster" therapy were compared with the experience of the same patient during primary therapy, we were impressed with the adequacy of anamestic treatment. In the ragweed group, 83 per cent procured results that were entirely satisfactory to the patient and to ourselves. In the timothy group, 80 per cent were in this category.

2. Anamnestic therapy was usually accomplished with five to six injections in a two to three week period, instead of thirty to forty injections spread over a three to six month period in preseasonal therapy. This is an important saving in time, money and effort for the patient.

3. Primary therapy over a sufficient period of time to assure a maximum immunological response, followed by anamnestic therapy just prior to the appearance of atmospheric pollen in future seasons, seems to be a satisfactory method of managing pollen disease.

4. Systemic reactions were no more frequent in the anamnestic group than in the control group of perennially treated patients.

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THE TREATMENT OF ALLERGIC HEADACHE

(Continued from Page 615)

ture, in addition to the benefits obtained by avoidances, hyposensitization, et cetera.

It is probable that many headache patients are "conditioned" in such a way that they are predisposed to frequent attacks. Such attacks may be initiated by a chain of events or circumstances. A frank discussion of this possibility with the patient may aid in guiding him to recovery. In such a discussion, the mechanics of the conditioned reflex could be described as an illustration. It may be even necessary to change certain of the patient's routines which are associated with the onset of headache.

CONCLUSIONS

1. An impressive percentage of cases of frontal headache are relieved by the ergotamine drugs. This suggests, along with the symptomatology, the vascular nature of this type of headache.

2. Frontal headache may be associated with respiratory allergy; therefore, if this is present, it should be correctly managed.

3. Food sensitization may be a factor in many cases. Direct food tests may prove sensitization to foods.

4. There should be a better liaison between the psychiatrist and the allergist.

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The Editor's Page

"WHAT'S good for poison ivy?" is a question put to every physician in the field of allergy. Hoagland[7] and his colleagues attempted to evaluate six remedies in ninety-two patients with 217 involved areas, applying two treatment substances to two equally involved areas on the same subject. In fifteen of twenty-seven so treated with Pyribenzamine cream and Nupercainal ointment, the results were equal. In ten of these, the 2 per cent Pyribenzamine cream appeared to accelerate healing, although only slightly; and in two, Nupercainal ointment seemed to help the lesion to some degree. In twenty-one of twenty-five others, treatment with PBZ cream and Rhulitol gave equal results, with two responding slightly better to Pyribenzamine cream and two others to Rhulitol. Twelve subjects who were treated with 2 per cent zinc sulfate and with Rhulitol responded with six finding the drugs equal; but in four, Rhulitol was superior and in two, zinc sulfate seemed superior. Eight others were treated with Neoxyn and zinc sulfate, and five with Neoxyn and Rhulitol. There was no difference in the healing time. Of the drugs used, zinc sulfate, Neoxyn and ethyl chloride spray were least effective, and the other three drugs were approximately equally effective, but none could be said to cause dramatic or quick recovery.

On the other hand, Cronk and Naumann[6] reported that an ointment containing Zirconium oxide (4.37 per cent) with stearic acid (13.46 per cent), potassium hydroxide (1.86 per cent), glycerol (2.28 per cent), and water (78.03 per cent) caused an improvement within twenty-four hours in thirty-nine of forty-six patients with poison ivy dermatitis. In two volunteers, immediate application of the ointment to areas painted with a 1:10 dilution of *R. toxicodendron* extract prevented the development of a dermatitis.

Barail[2] recently reported on an intradermal test for contact dermatitis. The technique consists of shaving an area on the side of the spine of an American chinchilla rabbit. Dilutions of the cosmetics to be tested are injected (0.5 cc.) intradermally into the area at points one or more inches apart. Examination of the area in twenty-four hours reveals the presence of any primary irritant, and retesting ten to fifteen days later helps elicit the sensitizing properties of the test substance. The author states that the accuracy and degree of reliability of the intradermal test is as great as that of the United States Public Health Service Patch Test.

Three cases of purpura as a manifestation of penicillin sensitivity are reported by Criep.[5] In these subjects, the Rumpel-Leede tourniquet test was positive. The hematological studies revealed no abnormality of

bleeding or prothrombin time or clot retraction. There was no platelet deficiency. The purpura was diagnosed as vascular in origin.

Allergic purpura as responding to Chlor-Trimeton was reported by Adams and Sacca.[1]

In a review of a case report of erythema multiforme exudativum, Chipps[4] discovered that Pyribenzamine and aureomycin were without effect. On the other hand, in a case report by Bleier and Schwartz,[3] aureomycin caused subjective improvement and a fall in temperature following its administration in 250 mg doses every four hours for seven days. Aureomycin ointment was used locally. When new bullous lesions appeared, cortisone was used in 100 mg doses every eight hours with clearing of the skin and the conjunctiva within forty-eight hours and of the balanitis by the sixth day. Four months following cessation of cortisone treatment, the patient was still well.

Jacobs[8] treated a group of chronic eczema patients with phthalanilic acid. He discovered that in a series of twenty-six successive subjects, whose chief complaint was chronic eczema, eight showed large skin reactions to *E. coli.* These were treated with phthalanilic acid, 3 to 4 gm daily, with a striking improvement, the skin clearing in two to twenty-four weeks. Cessation of treatment was followed by a relapse, and resumption of treatment, by remission. One patient not sensitive to *E. coli* was unchanged by the treatment.

Sternberg[9] and his associates have some fundamental work in the field of atopic dermatitis. They were able to place seven normal and eight atopic dermatitis patients into a room maintained at 100 to 110° F, and 90 to 95 per cent humidity, for one hour. The normal individuals showed a 55 per cent decrease in eosinophilia, while the eight atopic subjects demonstrated a 47 per cent increase in eosinophil cells. It is suggested that the abnormal response of the atopic individuals may be due to hypothalamus derangement, or to an abnormality related to the adrenal medulla. It has previously been known clinically that allergic individuals are unusually sensitive to changes in temperature. Laboratory corroboration sets further investigation upon the right track.

It has often been said that if a patient suffering from pruritus ani can, for one single moment, think of any other subject, the diagnosis is not pruritus ani. Of interest, therefore, is the work of Turell,[11] who reports that a starch, or tar, bath followed by the application of 1 to 3 per cent Trimeton ointment results in relief, although the pruritus recurs following cessation of treatment in more than 40 per cent of the patients. Only eleven of his forty-two patients were allergic. In fifteen others, relief followed the topical application of an aqueous cream base containing sodium caprylate and sodium propionate, each 5 per cent. In seventeen patients recalcitrant to treatment, perianal tattooing with mercury sulfide was necessary.

The importance of accurate statistics and the great part played by psychogenic factors in the clinical evaluation of any drug is highlighted by a significant study by Stolte.[10] To determine the effect of the drug used for the treatment of peptic ulcer, forty-nine patients were given the medication, and fifty-two, a placebo, neither the patient nor the physician knowing which was which. Of those who took the drug by injection for duodenal ulcer, 93 per cent were benefited, while oral medication helped 70 per cent in this group. In those suffering from gastric ulcer, the comparable figures were 78 per cent and 60 per cent. The percentages for both groups were, therefore, 86 per cent and 66 per cent.

Unfortunately for the experiment, the group given the placebo medication also improved, with 75 to 78 per cent becoming symptom-free. Of the twenty-four gastric ulcer patients receiving placebo medication, the improvement was confirmed in twenty-one by x-ray studies, which showed either marked reduction in the size of the ulcer, or its complete healing. The "inevitable 75 per cent" seen over and over again in clinical evaluations should, in most cases, be taken as the lowest limit for the results of placebo medication.

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Progress in Allergy

EXPERIMENTAL ASTHMA

Critical Analysis of the Literature

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STUDIES WITH INHALANTS IN THE LOWER ANIMAL

As far back as 1911, Friedberger[27] succeeded in producing in guinea pigs what he called anaphylactic pneumonia by subjecting animals that had previously been sensitized to horse serum to a spray of this substance.

Busson[11] sensitized the air passages of guinea pigs by having them inhale diluted cattle serum.

Sewall and Powell[70,71] sensitized animals by the nasal instillation of horse serum. They further demonstated that after continued exposures the animals developed symptoms of bronchial asthma. His findings led Sewall[69] to state that because he had produced all the features of bronchial asthma in the guinea pig in accordance with the criteria set for the anaphylactic phenomenon, he believed that the origin of this asthma is anaphylactic. The condition he had produced in the animals was the result not of a local hypersensitiveness, but rather of a generalized one.

Arloing and Langeron[3] made an inconclusive attempt to expose sensitized animals to shock experiences via the respiratory tract with homologous and heterologous antigens. Their experiments and criteria are subject to question.

In 1920, Besredka[5] showed, for the first time, that serum introduced into the larynx is harmless for normal animals but fatal for sensitized ones. He stated that it is comparable to the intravenous introduction of serum and suggested the use of a concentrated serum by this route for therapy in man.

The work of Petragnani[51], who sensitized and produced shock in guinea pigs with sheep serum by way of the nasal mucosa, is especially interesting because he was concerned with the prevention of seepage of the instilled serum through the laryngotracheal passages. The serum was introduced into the nares while the animal was held in an inverted position.

Busson and Ogata[12] adhered strictly to the use of horse dander in solution, which was introduced into the animal cages in the form of a heavy spray. After prolonged spraying for many days, death ensued in the animals, preceded by a fall in temperature and with typical evidence of anaphylactic lungs.

Writing in 1924, Sternberg[76] expressed the belief that Petragnani was the only investigator to show absorption of a colloidal substance through the nasal mucous membrane. He did not seem to consider the work of Besredka, Busson and Friedberger of significance because they did not prove whether the material introduced was taken up by the mucous membrane of the upper respiratory tract or by the mucous membrane of the alveoli of the lung. From his own work he inferred that colloidal protein is not absorbed to a noticeable degree via the healthy mucous membrane of the trachea, but rather by the alveoli of the lungs.

Jones[37] was able to sensitize guinea pigs intratracheally with small amounts of horse or cow serum, but he was not able to produce shock by intratracheal injections. He was of the opinion, therefore, that small amounts of foreign serum are

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absorbed slowly through the lower respiratory tract, and he felt that this might account for his inability to produce shock by intratracheal injections.

Alexander and his coworkers[1] used dander extract solutions in their inhalation experiments. They followed the method of Busson, introducing the heavy spray into the cages. Sensitized animals died within one to five minutes after inhalation of the sensitizing substances. They fully corroborated the work of Friedberger, Busson, Sewall, and Petragnani, and made a further contribution to this problem by demonstrating that some of the dander extract was present in the substance of the lungs.

In 1937, Kallos and Pagel[39] did extensive investigations with the inhalation of atomized antigens, both as sensitizing and as shocking agents. Their description and discussion of the pathology of experimental asthma, which will be discussed further on, is especially noteworthy.

Neely[47] induced symptoms in sensitized guinea pigs by the forced inhalation of a vaporized solution of egg white. He noted that the symptoms in the sensitized animals resembled those of human asthma, except that their onset and subsidence were more rapid.

From their observations on animals placed in a closed chamber in which either swine, rabbit, goat or horse serum or egg albumin solution was continuously atomized, Hopps and Moulton[33] concluded that active sensitization can readily be accomplished by inhalation of finely atomized fluid antigen and that serious allergic reactions, even fatal anaphylactic shock, may occur when hypersensitive animals inhale aerosol of specific antigen.

Sensitization and Shock Induced With Dry Antigens

Ulrich[82] in 1918 was the first to attempt to sensitize guinea pigs with a dry antigenic substance. He was mainly concerned with the problem of hay fever and used ragweed pollen for his experiments. He insufflated dry ragweed pollen into the nares of guinea pigs and concluded that the clinical manifestations of hay fever could be reproduced in laboratory animals.

The experiments of Friedberger and Kamio[28] in 1923 interested us considerably. They sensitized animals with dander extract and then attempted to produce shock by subjecting them to a spray of dry horse and cattle dander. They failed to accomplish their objective.

Busson and Ogata criticized their work, contending that the animals had been exposed to the dry dander for too short a period, but made no attempt to carry it on farther.

In 1924, van Leeuwen and his associates[83] reported that they had succeeded in sensitizing animals by the inhalation of parasite-infested oats. They also claimed that their animals manifested allergic symptoms shortly after contact, that is, within three or four days after their first exposure to the contaminated oats. They suggested that an asthmogen, and not an anaphylactogen, was responsible for the symptoms. These authors considered the possibility that the reaction manifested by certain animals on first exposure might be attributable to the toxicity of the material, but expressed the belief that it was more likely that the animals were previously sensitized because of the ingestion or inhalation of infected grain or straw.

Quoting some unpublished work that he did with Landsteiner, van Leeuwen stated that they had been unable to produce shock in previously sensitized animals by the inhalation of pollens and dried horse serum. It may very well be that the choice of these two antigens was unfortunate because of the low antigenicity of pollen and the extremely doubtful antigenicity of horse serum when used in a dry state.

This essentially was the background when we undertook our investigations. We were not convinced that liquid antigens provided the ideal medium for the modification of the anaphylactic method to bring experimental conditions closer to those

present in man. Though the studies with the inhalation of dry antigens were inconclusive, we still felt that this was the approach which should be used. We were confronted then with the problem of devising a technique which would enable us to sensitize and shock animals solely through the inhalation of a dry antigenic dust in a natural manner, yet conforming to the other criteria of true anaphylaxis.[64]

For this purpose, we[57] contrived an inhalation chamber which we believed provided for the guinea pig an environment similar to that which a human being encounters in a dust-laden room. We made provision for gentle circulation of the dust, yet provided adequate ventilation. The chamber was so constructed that we had an unobstructed view of the animals.

In our work, we adhered strictly to the use of a dried dander which was devoid of fat but in no other way changed metabolically. It might be argued that the defatted dander is different from the dander inhaled by a person in a natural contact. However, in a series of experiments[64] we showed that the fat extracted from the dander was not anaphylactogenic; hence we feel it is reasonable to assume that nothing of antigenic value was lost by the extraction. The fat and heavier particles that were removed, it may be conjectured, are more the result of the intense combing process to which the animals are subjected in grooming. Our dried dander might therefore be more nearly comparable to the lighter particles of naturally occurring dander which would float in the air and with which an individual actually does come in contact.

The data in our original experiment demonstrated that animals are not easily sensitized by exposure for one quarter to one half hour. Less than fifty per cent of the animals which inhaled dander for one to three hours were sensitized. However, those that were sensitized were profoundly affected and died in anaphylactic shock when given the intravenous injection.

Of eighteen animals exposed for four to five hours, the overwhelming majority were profoundly sensitized.[57,62]

In successive stages we then proceeded to show that in animals previously sensitized by parenteral injection, we could induce shock symptoms by inhalation. Finally, by combining sensitization and shock experiences solely through inhalation, we reproduced in our animals a respiratory anaphylaxis that bore sufficient analogy to the asthmatic syndrome in the human being to enable us, we believed, to refer to it as "experimental asthma." Sewall (1917) too had designated the symptoms noted in his animals as "experimental asthma in the guinea pig."

Subsequent studies[57] led us to draw the following conclusions:

1. Guinea pigs exposed to a dry antigenic dust are sensitized with great frequency if exposure is adequate. Five to seven hours seems to be the optimum period.

2. Animals sensitized by inhalation have attacks of asthma of varying degrees of intensity when subsequently exposed to the specific dust. For the most part they react each time they are exposed and do not manifest the classic antianaphylactic state observed after repeated parenteral injections. However, in certain animals the response is not constant and refractoriness is observed during some exposures. This train of events resembles the sequence of attacks in human bronchial asthma and in status asthmaticus.

3. Certain animals appear to remain unaffected in spite of repeated exposure. Whether this resistance is relative or absolute we are not prepared to state. As the source of supply and the factors of weight, age, type of exposure, and nature of the antigen were the same, the differences exhibited by the animals, with respect to the readiness and rapidity with which sensitization was established and the severity of their reactions, appear to be due to the amount of exposure and to certain inherent attributes of the individual animals.

4. Although the experiments reported[60] were not sufficient to permit final conclusions, it appears that when the sensitizing agent is a dry antigenic dust, sensitization may be regional, involving the respiratory structure alone, or may be more extensive, involving other organs. The regional condition is comparable, we believe, to human inhalant allergy with negative endermal reactions.

5. The fetus may be either actively or passively sensitized by the pregnant female's inhalation of the dry antigenic dust.[63] We had instances in which sensitization was more profound in the mother than in the offspring, and, conversely, instances in which the offspring had a higher degree of sensitization than the mother. Kallos and Pagel report similar findings.

Further studies showed that inhalant sensitization may be accomplished with an antigen other than horse dander, for example castor bean dust.[61] We also demonstrated that a guinea pig sensitized by the inhalation of horse dander dust may become sensitive to the homologous horse serum.[58]

In the course of our experiments we determined that the administration of epinephrine successfully relieves the asthmatic symptoms in the animal.[64]

The anaphylactic symptoms demonstrated in the animals of Sewall, Petragnani, Busson and Ogata, and Alexander et al, as a result of the instillation and spraying of liquid antigens, do resemble the clinical symptoms manifested in a person with asthma. However, because we used a dry antigen to carry out both aspects of the experiment, i.e., sensitization and shock, and because we believe the experimental conditions set up are more consonant with conditions presented in the human subject, we feel that the method described does produce an experimental syndrome in the guinea pig which closely parallels human inhalant asthma and pollinosis. This method offers wide possibilities for detailed investigation of phylactic and prophylactic measures in the human subject.

Certain investigators have since worked with dry antigens, with what they regarded as equivocal results. (Chase;* Leith, Leger and Rose[41])

Tai[79] shocked animals that had previously been sensitized to bovine serum by the intratracheal insufflation of powdered bovine serum. He contended that because of the slow absorption of the inhaled antigen, a high degree of sensitization is required to demonstrate anaphylaxis. His difficulty may have been the employment of a dried serum which essentially has a low degree of antigenicity and is of large particulate size, not readily dispersed or diffused.

More positive corroboration of our work is found in the experimental studies of Courtright et al.[21,22] They followed our methods in all details and agreed with us that the inhalation method approaches more closely natural sensitization in man, reasoning that

(1) the allergen must enter the body through the nasal and respiratory membrane;

(2) sensitization is built up by repeated exposures which approximate more closely clinical sensitization;

(3) the respiratory membranes, because of repeated exposure, may acquire resistance to general sensitization which may not result from subcutaneous or intraperitoneal routes.

They amplified the work by studying inhalant sensitization under controlled meteorologic conditions. When they exposed the animals in a dry, hot atmosphere and ground the dander to a smaller particulate size, a larger number of animals died as compared with our series in which animals were exposed in room air.

*Merrill W. Chase, in a personal communication April 28, 1948, with reference to some preliminary and unpublished experiments using our method, stated: "The experimental setup was not entirely satisfactory, but as you will see (from the protocols) the results indicate that inhalation-sensitization followed by inhalation testing gives mild but positive symptoms, whereas extract-sensitization followed by inhalation-testing gave strong and usually lethal anaphylactic effects."

The dander first prepared by our method was further treated by being placed in a ball mill for eighteen hours.

Prausnitz[54] exposed guinea pigs for many months to dry cotton dust by a method similar to ours and produced chronic conditions resembling "cotton operative's asthma." He demonstrated the presence of cotton dust in the alveoli of the guinea pigs that had inhaled it in a natural manner.

Locus of Contact and Absorption

Liquid Antigens.—Petragnani instilled antigen intranasally in the guinea pig, holding the head in an inverted position. He also produced shock intranasally in tracheotomized animals. During the course of such injections in tracheotomized guinea pigs he never saw the serum issue from the upper cut section of the trachea, no matter with what force the antigen was injected. The excess passed into the buccal cavity or the esophagus. He concluded that the material was absorbed solely by the olfactory cells and the olfactory pharyngeal mucosa.

Working with cats, Blumgart[7] found that crystalloids and colloids traverse the nasopharynx and are absorbed by way of the olfactory nerve cells to the systemic lymphatics.

Busson sprayed serum mixed with India ink into the nares of guinea pigs and found particles in the lung parenchyma.

Alexander et al, however, have presented the most concrete evidence for the demonstration of serum in the alveoli. They removed and macerated the lungs of animals, shocked by spraying, carefully separating the lungs from the trachea. This material provoked a positive reaction in a sensitized uterine horn. Jones[38] also demonstrated serum in the macerated lungs of guinea pigs by means of the precipitin test. The serum was injected via the trachea.

Besredka, and Renon and Mignot[65] used serum that was concentrated ten to twenty times for their experiments. One hundred grams of dried serum were dissolved in a syrupy concentrate consisting of 250 cc of serum. No shock ensued when this was injected into the larynx. The material was dissolved slowly and served to sensitize animals, but they were not easily shocked.

Jones's[37] studies refuted the conclusions of Besredka and Ishioka[35] that the trachea serves as an organ of absorption. He clearly showed that the intact trachea is signally impermeable to the passage of colloid material and that the alveoli serve as the absorbing membranes. Absorption through the lung, however, is extremely slow, taking several hours longer than absorption by way of the intraperitoneal route.

Sternberg never found colloidal dyes (carmine and collargol) in the nasopharynx after swabbing. They seeped down to the alveoli. The fact that small amounts were absorbed locally by the nasopharynx he attributed to mucosal defects. In dogs, he showed further that the urine turned green after nasal swabbings with argochrome, and he ascribed the change in color to the absorption of the argochrome through the alveoli.

Kallos and Pagel make the point that the particles must be less than 0.005 mm in diameter in order that the drops may penetrate into the alveoli of the lungs.

It was shown by Mullin and Ryder[46] that suspensions of India ink introduced into the nostrils of rabbits readily entered the lungs and even the terminal bronchi and alveoli when these animals were placed in a recumbent position. These experiments were amplified by Corper and Robin[20] who showed that the distribution of particulate materials within the lungs is determined primarily by posture. They found that if India ink was instilled intranasally in rabbits and dogs in the horizontal position under ether anesthesia, the material localized mainly in the upper lobes of the right or left lung, depending on the side on which the animal was lying. When the animals were kept in the vertical position, the ink tended to

localize in the lower lobes. They concluded that "these observations strongly favor the idea that the localization of aspirated fluids in the lungs is largely determined by physical forces such as gravity and inspiratory suction."

Cannon and Walsh[13] repeated these experiments by instilling India ink or trypan blue into the nostrils of normal rabbits or normal guinea pigs. When the rabbits were held on their feet, with the head slightly elevated, the particulate material reached the lungs and localized predominantly in the upper lobes or upper pulmonary regions. When the animals were held on their sides, in the horizontal position, the ink localized in the upper lobes of the dependent side, whereas if they were held in the vertical position the particulate matter tended to accumulate in the lower lobes. These results confirmed those of Mullin and Ryder, and Corper and Robin in all essential respects, with the additional evidence that even in unanesthetized rabbits in the horizontal position the particulate materials usually, although not invariably, entered the lungs.

These observations lend further support to the work of Petragnani.

Dry Antigens.—In order to obtain uniform shock results, one must use finely sprayed material or finely powdered dusts. Great stress has been laid on this point by the majority of successful investigators in this field.[1,11,21,39,44,54,77]

Prausnitz prepared his dust by shaking through various sized sieves. He stated that ultramicroscopic examination of the dust floating in the air after a sample of cotton had been beaten revealed that there was practically no lower limit to the size of the dust particles. The greater amount of the "fine dust fraction" actually consists of ultramicroscopic particles, i.e., of a size under 0.2 microns. It is clear that they will readily be inhaled into the finest and deepest portions of the respiratory system. They were even so fine, he continues, as to be able probably to pass through the alveolar wall into the interalveolar tissue. Their relatively large surface will allow any of their constituents which are soluble in the alveolar mucus and in the intercellular lymph to enter into solution, as the case may be, in or beyond the alveolar surface.

Though we were signally successful in our experiments, which extended over a number of years and which entailed the use of many animals, we do believe that working with dry antigens will undoubtedly offer many more difficulties than spraying with liquid antigens. In the first place, the preparation of the material is more of a problem. It must be presented to the animals in a dry, undenatured state, in powdered form the individual particles of which must be very small; and it must be easily dispersed, dissolved, and absorbed by the animal membranes. If these conditions do not obtain, inhalation is impeded and absorption will either be delayed or will not occur at all. This is in marked contrast to the liquid aerosols which are presented in a fine nebulized spray and are readily absorbed by the nasal mucosa and respiratory tract. Materials that are too coarse may help to explain the failures of certain investigators to sensitize their animals with horse and cattle dander, dry pollen, and dry horse serum. For the purposes of our experiments the horse dander and castor bean dust, defatted in preparation, was so fine that it passed through a 200-mesh sieve.

Observations of Barclay, Franklin and Prichard[4] on the fate of inhaled dusts are of value. They used cats for their experimental subjects and radiopaque dusts, such as powdered lead glass, bismuth carbonate, and uncompressed gas flame carbon for their inhalation materials. These dusts were introduced by direct insufflation, inhalation during quiet respiration, and inhalation during spasmodic respiration. All of the anmals were found to have dust within the alveoli, as studied by roentgenography.

They excised the lungs and trachea, which were immediately roentgenographed. All the animals were found to have dust within the alveoli. Although the amount

of alveolar dust varied much, it was never so great as to be detectable with certainty in the roentgenograms. This is in marked contrast to the obvious bronchial dusting. The amount of alveolar dust did not run parallel with the amount of bronchiolar and bronchial dusting. Almost identical quantities of a particular dust could be present in the alveoli of two subjects, yet the bronchioles and bronchi of one were loaded and of the other practically clear. Regardless of the methods used in the experiments, the amount of dust in the alveoli is about the same. Introduced dusts appeared to collect in relatively greater amounts in inflamed portions of lungs.

The authors believe that the loaded alveolar dust cells move toward the ciliated epithelium of the bronchioles, are caught up on the layer of viscid mucus, and are carried up with it by the action of the cilia. The dust brought up into the pharynx is swallowed and passed out by the alimentary tract.

The outstanding feature of this work was the demonstration of the apparent existence of a defense mechanism preventing the entry of large quantities of dust into the alveoli, for the total quantities in them were comparatively small even when the bronchioles were heavily loaded.

Pulmonary Arthus Phenomenon

Ströbel[77] noted that serum injected into the trachea did not cause general anaphylaxis, but on the day following the injection he found a typical pneumonic exudate, which he likened to the Arthus phenomenon.

Busson also found that four days after sensitized animals were sprayed they showed hemorrhages and infarcts; like Friedberger, he expressed the opinion that it was due to pulmonary anaphylatoxin.

Opie[49] reproduced the phenomenon of Arthus in the lung of an immune animal. Injection of 0.2 cc of horse serum through the thoracic wall into the lung of an immunized rabbit caused localized consolidation, with leukocytes and edema surrounding a central focus of necrosis. The same antigen injected into a normal animal was absorbed from the lung with no noteworthy change.

Fried[26] reported that rabbits sensitized by repeated intraperitoneal injections of horse serum contracted acute lobar pneumonia when the last injection was introduced into the lungs via the trachea.

SUMMARY

Anaphylaxis induced through inhalation, as we have shown, differs from the parenterally induced form in several respects. The differences are largely due, we believe, to the character of the antigen used, the manner of its presentation to the host, the locus of contact and absorption.

From the evidence presented it would seem: (1) the trachea is not an organ of absorption; (2) both the nasopharynx and the terminal pulmonary units may serve as absorbing and reacting areas, whether the antigen is in a liquid or dry state; (3) both the liquid and dry antigens must be presented to the host as a finely divided aerosol; (4) the Arthus phenomenon may be induced by direct extension into the lung parenchyma either via the trachea or by injection.

Studies with Inhalants in the Human Subject

The experimental work on respiratory anaphylaxis thus far presented was carried out primarily in guinea pigs. The question might then be raised as to whether the mechanism in the guinea pig is fundamentally the same as it is in the human subject. We shall therefore examine the experimental work on the human subject which has been reported upon in the literature. In some instances it has been planned, and in others it has been the result of fortuitous circumstances.

Liquid Antigens

Dzierzgowski[23] and later Blumenau[6] actively immunized children to diphtheria toxin by the introduction of toxin-soaked tampons into the nares.

More recently, Jensen[36] recommended the use of intranasal instillations of diphtheria toxoid rendered nontoxic by incubation with formaldehyde (formol toxoid) as a complement to a single subcutaneous injection. He showed that the titer of diphtheria antitoxin in the blood was definitely increased in human subjects by this procedure.

Blumgart[7] similarly demonstrated that aqueous pituitary extract was absorbed through the nasal mucosa by the subject with diabetes insipidus and that this resulted in therapeutic improvement.

Work of a similar nature, but approached from a different point of view, was that of Simon and Rackemann.[72] Their aim was to show that hypersensitiveness can be established in human beings by absorption of antigens through the nasal mucous membrane. For this investigation absorbent cotton was soaked in guinea pig serum and inserted into the nasal cavity of the subject. The nine subjects, all sufferers from inhalant allergy, were free of symptoms at the time of the study. Applications of the serum were made at intervals varying from three days to two weeks or longer. Following the second and third applications, nasal symptoms developed in four cases. In five cases no nasal sensitization developed, yet in all nine cases positive cutaneous reactions were obtained when the subjects were tested three weeks to two months later.

Ramsdell[56] noted that the skin of normal human beings regularly shows the immediate type of reaction to normal guinea pig serum in a dilution of 1:10 (used by Simon and Rackemann) and to a lesser degree in a dilution of 1:50.

If the work of Simon and Rackemann is repeated with other substances, it will afford further conclusive proof that liquid antigens can be absorbed by the nasal mucosa and induce sensitization.

Absorption through the nasal mucosa was further demonstrated by Chait and Walzer[14] in human beings with peanut antigen.

Of interest is the unique experiment of Bonsfield and King-Brown.[9] They found difficulty in using the instillation method of Jensen and therefore resorted instead to finely atomized diphtheria toxoid. Adult volunteers were chosen. They were put into a room 15 by 12 feet (4.57 by 3.66 meters) for fifty minutes. Into this chamber an atomizer ejected the vapor at the rate of 1 cc per minute. The subjects frequently changed their positions in order to receive equal exposures. They were exposed for two periods two weeks apart. Reactions following the first inhalation were negligible, but after the second they were rather severe in most cases, which was attributed to allergic sensitization. Headache, chills, fever, tightness of the chest, and cough were the symptoms presented. The antitoxin content of the blood was considerably raised in each instance. This work was corroborated by Wenger et al.[85]

Dry Antigens

It has been known for many years that industrial workers become sensitized to dry antigenic substances which they inhale. Among these may be cited veterinarians, grooms, and cavalrymen who become sensitized to animal dander; millers and bakers to meal dust; apothecaries to ipecacuanha; quinine factory workers to quinine; and coiffeurs, wigmakers, dealers in fur skins, and animal keepers to hair. Ubiquitous substances, such as pollen and environmental dusts, give rise to symptoms in young as well as in older patients.

Several studies have appeared which emphasize factors of interest. For example, Colmes, Guild and Rackemann[18] studied a group of bakers and showed that about 40 per cent became cutaneously sensitive, although only one was clinically sensitive.

This group worked in a scientifically controlled baking establishment, which may account for the infrequency of the clinical symptoms.

Salen and Juhlin-Dannfelt[67] tested a large number of persons belonging to different occupational groups. They found that on cutaneous test those exposed to occupational allergens reacted to the respective allergens more frequently than controls who were of different occupational groups. These results were interpreted, by the authors, to indicate that a positive cutaneous reaction to an allergen to which one is exposed may imply a latent allergy if no symptoms are manifested.

Blumstein[8] reported on nineteen patients skin-positive to buckwheat, of whom only eight were clinically sensitive. Most of the patients, however, reacted after inhalation but showed no symptoms on ingestion of buckwheat. The fact that they did not react on ingestion may be due to the change in the allergenicity of the buckwheat due to cooking (Ratner and Gruehl[59]).

Cohen and his co-workers[17] presented the most exact experiments thus far made with respect to the nasal absorption of dry antigens in human beings. They used both normal and allergic subjects. The method employed was to sensitize a site on the arm passively with serum obtained from a patient allergic to ragweed. Twenty-four hours later dry pollen was insufflated into the nares, care being taken to have the patient avoid swallowing the material. The antigen was absorbed into the blood stream, as judged by the appearance of a wheal at the prepared site.

Intranasal absorption occurred in all of fifty normal subjects studied. The reaction appeared within fourteen to thirty-one minutes, an average of 21.8 minutes.

In persons with inhalant allergy, the rate of absorption ranged from eighteen to sixty-nine minutes, an average of 41.9 minutes. This was demonstrated for seven of twelve allergic persons. No reaction occurred in the remaining five patients during the period of observation, which varied from sixty-five minutes to two hours. When the pollen was insufflated in patients sensitive to ragweed, a severe local nasal reaction occurred. No ragweed pollen could be demonstrated in the blood of such subjects after three hours of observation. The interesting point is that allergic subjects showed marked delay or even an absence of absorption.

Cohen et al[16] subsequently demonstrated by an ingenious method that intranasally absorbed antigen remains in the circulation for a period not exceeding twenty-four hours.

The work of Cohen and his co-workers is of fundamental value in proving that a dry antigen can be absorbed by way of the nasopharynx in practically any normal person. The failure of absorption in specifically allergic subjects, in whom a severe local reaction develops through direct local contact with the allergen, may be correlative to Opie's work[48] which showed that inflamed tissues tend to retain injected antigen. The delayed absorption observed in allergic persons sensitive to substances other than pollen may be explained on the basis of diminished permeability due to the thickened basement membrane of the mucosa—an almost universal attribute of chronically allergic tissue, both nasal and pulmonary.

Leopold and Leopold[42] induced attacks in human asthmatic subjects with specific antigenic dust introduced into a dust-free chamber.

Probably the most intriguing group of studies were those made with silk. It was not generally known that silk contributes many air-borne particles in the modern household until the work of Figley and Parkhurst[25] appeared. They demonstrated conclusively that silk—or, more correctly, the gum or glue of the silkworm secretions present in the silk—exerts its effect as an inhalant rather than as a contactant in producing eczema.

Sulzberger and Vaughan,[78] utilizing the technique first employed by Cohen and his co-workers, confirmed the observations of Figley and Parkhurst. Dry silk powder sniffed into the nostril was absorbed directly into the blood stream. The absorption time was approximately that found by Cohen with pollen (twenty minutes). Thus Cohen's work on the absorption of dry antigens through the respiratory tract was

corroborated, and the careful clinical observations and conclusions of Figley and Parkhurst were fortified.

Endemic Asthma

To Ancona[2] must go credit for describing what may be called endemic asthma. The cases occurred among millers in a small village in Italy. They manifested symptoms of asthma associated with urticaria and dermatitis, which Ancona traced to sensitization from wheat which was infested with *Pediculoides ventricosus*. The outstanding feature was that only those who sifted and ground the infected wheat for long periods became sensitive. No particular family disposition was found. Unrelated persons who worked in the granary became affected, whereas their relatives who remained at home or worked at some other occupation were unaffected. The attacks occurred shortly after or during the shoveling, sifting, or grinding of the damaged grain. Experimentally Ancona produced the hemoclastic and asthmatic crisis by having the sensitive person inhale the dust of the damaged grain, and he also obtained positive cutaneous and intradermal reactions with it. The dust of the sound grain was innocuous.

Van Leeuwen, Bien and Varekamp[83] subsequently studied another form of endemic asthma in the lowlands of Holland. They attributed it to mite-infected oat grains. Because Cooke, Flood and Coca,[19] Friedberger and Kamio,[28] and they themselves were unable to sensitize animals to pollen, dry dander, and dry horse serum respectively by inhalation, van Leeuwen and his co-workers expressed the opinion that it is unwarranted to assume that true asthmogenic substances alone can produce sensitization. Stimulated by the work of Ancona, they suggested that the strong primary action of the contaminating mite so irritated the membranes of the respiratory tract that the rue allergen could then sensitize the tissues. They called the activating substance a miasmen. In sensitive persons, exposed to the inhalation of the contaminated grain when they were free from symptoms, there developed typical allergic symptoms and urticaria. Reactions to cutaneous tests with a water extract of the pure oats were negative. Tests with an extract of the mites, as well as with the oat residue freed from mites, gave positive reactions. The authors concluded that the reactions were due to the metabolic products of the mites in the oats. Cases of allergy were cited in children who slept near bins containing the infected grain, and in farmers and merchants handling the grains, flower bulbs, and straw. Van Leeuwen and his associates compared this type of miasmen with paraphenylenediamine, a factor in tanner's asthma, and to emetine in the ipecacuanha-sensitive individual. He went so far as to assert that sensitivity to bread and other meal-containing foods may be due to contaminated grain and that horse dander sensitivity may be due to mite-infected straw which gets into the horse's hair in the stable.

The next example of endemic asthma, reported by Figley and Elrod,[24] occurred in the vicinity of a castor oil factory. Persons who worked in the factory or who were within a mile of it were sensitized to the castor bean dust ejected from the chimneys. A large group of children in a school opposite the factory were affected. Housewives and children had their attacks at any time during the day or night. Sensitized persons living in this vicinity but working elsewhere had their attacks only at night, on returning to their homes. These authors proved their thesis by obtaining positive cutaneous reactions to castor bean.

Actuated by these observations, Ratner and Gruehl[61] obtained castor bean dust (pomace) from the same factory for experimental purposes.

Here, too, a primary toxic substance is present, namely ricin. Animals died within from one to nine days after inhalation of pomace from typical ricin poisoning involving the adrenals and intestines and also the lungs, in which hemorrhagic pneumonitis was observed.

On removing ricin from the pomace, we were able to produce all the symptoms of experimental asthma. The experiments showed the dual nature of the castor bean seed, which contains both a primary toxic element and a purely anaphylactogenic element. Interesting instances gathered from the literature illustrate sensitization of botanists, farmers, and others who handle castor bean dust. Castor bean is used as fertilizer.

Prausnitz[54] conducted an extensive investigation of the cotton industry in Manchester, England, as has been mentioned. He found that hypersensitiveness to cotton dust protein was regularly present in cotton operatives who were suffering from respiratory disease. In healthy cotton operatives similarly exposed the reaction was inconstant. It is interesting that one normal subject was artificially sensitized through an intracutaneous injection in the way that Simon and Rackemann[72] demonsrated with guinea pig serum and Hooker,[32] Park[50] and Tuft[81] with diphtheria toxin-antitoxin serum.

The active principle in cotton is derived from the dust protein of the husks; reactions were obtained with this material in a 1:100,000 dilution, whereas the protein from the cotton seed reacted only in a 1:10,000 dilution. No protein or reactions were obtained from the fibers. Prausnitz attributed a primary toxic reaction of the material to a histamine-like substance. Haworth and MacDonald[31] found that the histamine content of the blood of cotton operatives was higher than that of normal persons. This histamine-like substance is believed to be derived from molds which always contaminate cotton bales, much as Pediculoides infested the grain and mites infested the oats. Prausnitz, however, did not attribute the sensitization to the primary toxic substance, which may have been gossypol, but showed that it was due to the protein in the cotton dust.

It is of interest to note that most of the workers acquired their asthma after working in the cotton gins for many years; yet some, perhaps with greater susceptibility, acquired the disease in shorter time. Still others worked a lifetime at the same occupation but remained immune.

Endemic Pollinosis

Piness and Miller[53] cited the interesting situation of a group of city dwellers—mainly engineers—and their families, who were transferred to mountain communities. Thus these authors had the unique experience of studying the onset of hay fever in two comparatively young communities, the members of which were suddenly exposed to an atmosphere heavily laden with pollens that were largely different from those they had come in contact with in the past. A history of positive heredity was obtained in only 30 per cent of the cases. The great majority of patients began to have hay fever only after moving to these vicinities, and within the first few years of their residence.

Heredity seemed to play but little part in determining the interval which elapsed between the time that residence was taken up in the community and the onset of hay fever. There were persons who had a negative family history who developed hay fever after a short residence, and on the other hand individuals with positive family histories did not develop hay fever until after ten to fifteen years of exposure. The authors concluded from this that a superabundance of pollen might induce sensitization irrespective of heredity. Amongst the patients there were a large number of children ranging in age from one to ten years. This, Piness and Miller believed, was the result of an unusual contact at a particularly vulnerable period of life, rather than of an inherited susceptibility.

An even more striking example of endemic pollinosis was that studied by Phillips.[52] His paper concerns the behavior of a group of allergic persons when they were exposed in successive years to the pollen of sugar beet which they had never before encountered. This plant was introduced into Phoenix, Arizona, in 1935,

when a few experimental patches were planted. In 1936 the industry was actually introduced and 1800 acres were planted. The following year there were 3200 acres, and in 1938 the beet crop occupied 5500 acres, all of which went to seed. A considerable number of individuals who were never previously sensitive to sugar beet pollen began to develop such sensitivity. Phillips concludes that about two seasons of exposure to this newly encountered pollen was required to induce clinical sensitivity.

A number of papers have appeared showing the development of sensitivity to new pollens in the Pacific Zone amongst the members of the United States Army in the course of World War II.

It has been recognized, and confirmed by a study of Clarke and Leopold,[15] that Europeans coming to America, who have never previously suffered from ragweed hay fever, develop symptoms after an incubation period following initial contact.

That the experiments with the inhalation method in the guinea pig should be so closely paralleled by experiments, either planned or fortuitous, on human beings is corroborative evidence of the thesis that experimental asthma is an entity.

COMPARISON OF THE PATHOLOGIC PICTURE OF ASTHMA IN HUMAN BEINGS WITH THAT OF EXPERIMENTAL ASTHMA IN GUINEA PIGS

This brings us to another of the existing controversies. Some have held that anaphylaxis in guinea pigs and asthma in human beings cannot be compared because the basic pathologic changes differ. We propose to show that the error of this conclusion has been due to the comparison of bronchiolar constriction, which characterizes the pathology of the animal sensitized by parenteral injection, with the pathology of a sublethal inhalant allergy. Acute anaphylactic death in the guinea pig can strictly be compared only with acute anaphylactic death in the human being as described in the reports by Boughton[10] and others, in which instances the lungs were completely emphysematous, owing to bronchoconstriction.

On the other hand, if the pathologic changes of asthma are compared with those found in guinea pigs subjected to repeated inhalation of specific antigens, then only are similar phases of the allergic phenomenon being considered, namely, chronic allergic states in both species.

Pathologic Picture of Human Bronchial Asthma

We will first consider the features of human asthma, ably described by Huber and Koessler[34] and later by Kountz and Alexander,[40] Steinberg and Figley,[75] Harkavy,[30] Rackemann,[55] Wright,[86] Steinberg,[74] MacDonald,[43] Michael and Rowe,[45] Gaddum,[29] Thieme and Sheldon[80] and others. Briefly stated, the pathologic picture in patients dying from asthma comprises the following changes:

1. emphysema, lobular or universal,
2. edema of the bronchial wall,
3. sacculation of the epithelial layer of the bronchi,
4. hypertrophy of the bronchial musculature,
5. thickening and hyalinization of the basement membrane of the medium-sized bronchi and occasionally of the bronchioles and large bronchi,
6. increase of mucus in the bronchial and glandular lumens and mucous plugs in the large and medium-sized bronchi,
7. hyperplasia and hypersecretory activity of the goblet cells of the bronchi and mucous glands,
8. degenerative changes of the cartilage cells of the bronchi,
9. eosinophilic infiltration of the bronchial wall, peribronchial tissues, subepithelial layers and, at times, the bronchial lymph nodes and alveoli,
10. bronchial and bronchiolar stenosis caused by the exudative and bronchomuscular systems.

Thieme and Sheldon discovered that in cases of prolonged intermittent asthma in which death resulted from some intercurrent disease the pathologic pulmonary features were never *in toto* those of status asthmaticus. The one constant indication of previous asthma observed in the lungs was the hyaline thickening of the basement membrane.

Pathologic Picture of Experimental Asthma

To Busson[11] must go the credit not only for successful initiation of the inhalation experiment in 1911 but for presenting a comparative study of the pathology of anaphylactic death from intravenous injection and the pathologic-physiologic changes which ensue when animals manifest anaphylactic reactions to repeated sprays of antigenic liquid. In an animal killed by an intravenous injection, Busson found exclusively the markedly distended alveoli resulting from bronchoconstriction. A similar pathologic condition of the lungs was found in animals that died from a single spraying.

After repeated sublethal reactions the first effect is bronchial spasm, which leads to dilation of the alveoli and local hyperemia of the capillaries. This action is followed by edema in the alveoli and smaller bronchi, with increased secretion of mucus and perivascular infiltration of mononuclear cells.

Busson expressed the belief that the edema in the lungs is not compatable with anaphylaxis. The stenosis observed in the guinea pig and in the human being with bronchial asthma is therefore not exclusively the result of bronchial spasm in conjunction with edema of the mucosa and submucosa, which he correlated with changes observed in the sublethal inhalation reactions of guinea pigs.

In 1937 Kallos and Pagel[39] went further in the pathologic study of experimental asthma. They not only studied a group of allergically sensitized animals which inhaled sprayed antigen, but they drew a fine distinction between the conditions noted in such a group and those of a group treated with histamine and acetylcholine.

In the group treated with histamine and acetylcholine the changes in the lung are noncharacteristic. Besides chronic bronchitis, the most evident effects were the activation of the perivascular macrophages and the indications of severe disturbance of the circulation. Eosinophils played a certain but entirely subordinate role.

However, in the sprayed allergic animals, even after a single exposure, there was an enormous influx of eosinophils in the peribronchial and submucous vessels of the bronchi. At the site of the most marked migration of eosinophils were masses of mucous spheres, which increased in size and were then cast off into the lumen. The alveolar septa, as well, contained little nodules which consisted exclusively of eosinophils. These might completely fill the alveoli and present a picture of eosinophilic pneumonia. Besides these masses of eosinophils, there were marked edematous swellings in the walls of the smaller bronchi and in the alveolar septa; the basal membrane was thickened. Disturbances of the air content of the lung parenchyma were produced by these changes in the bronchi. Atelectasis was often combined with infiltration and splenization, together with variable emphysema. In general, the histologic changes in the animals were more marked the more often attacks had been produced.

Aside from the marked aggregation of eosinophils observed in the spleen in many cases, there were no interesting changes in the other organs of this group. Even the circulatory system was untouched. The latter observations are of particular interest because in asthmatic patients the heart is signally free from involvement (Kountz and Alexander). MacDonald, Michael and Rowe also observed that in human beings the only organ other than the lung which contained eosinophils to any extent was the spleen.

Kallos and Pagel concluded that the changes observed in this group of allergic animals after inhalation corresponded to those observed in the few reported cases

of chronic bronchial asthma in human beings in which autopsies were obtained. The principal changes in human beings—the enormous eosinophilic reaction, the mucous formation which develops into mucous degeneration, the swelling of the bronchial wall and of the basement membrane, and finally the secondary effects on the lung tissue (atelectasis, emphysema, and infiltration) which result in the thickening of the pulmonary framework—also develop in the experimental animal.

Kallos and Pagel stressed the importance of eosinophilia in experimental asthma. Similarly, Huber and Koessler stated that the chief cellular symptom of the allergic reaction in human beings is eosinophilia. In only one disease, bronchial asthma, does eosinophilia occur simultaneously in the blood, sputum, and tissue. The eosinophilic infiltration of the bronchial wall is a characteristic histologic criterion in asthma. Kountz and Alexander suggested that there is a special attraction between bronchial muscles and the specific allergens in asthma which results in excessive localization of eosinophils in and around such muscles.

The pathologic changes observed by Prausnitz in animals that were subjected to prolonged exposures to cotton dust are worthy of recital. These changes produced by inhalation of the dust over a period of three to thirty-six weeks were very pronounced.

In a normal animal, sections of lung show a typical reticulated appearance, the interalveolar walls being thin and delicate. Changes begin to appear after about a month in the dusted animals and consisted of the development of scattered peribronchial nodules. Soon after the nodules spread and coalesced, forming a peculiar thick network of the lung tissues. Instead of the string bag appearance, there now was that of a section through a thick rubber sponge. The alveoli, on the whole, remained patent in most of the animals, but there was a great thickening of the alveolar walls. This appeared to be due in part to edema, in part to infiltration with leukocytes and dust cells. In the animals which had been dusted for six months or more, practically the entire lungs had undergone this change. In addition, localized patches of chronic pneumonia were found in some animals, although during their lifetime pronounced signs of illness had not been observed. Under a higher magnification, the thickened alveolar walls were found to contain a large number of polymorphonuclear leukocytes, very many fine dust particles, and a small or moderate number of dust cells.

He maintained that histamine played a minor role and expressed the opinion that cotton dust has a great power of penetrating into the deepest parts of the lungs and of producing in them very extensive irritative changes.

This study was the first to give some idea of what may actually happen to human beings after contact with antigenic dusts for long periods. Prausnitz was unable to obtain any human material for post mortem study. It is a pity that he did not give a more detailed picture of the basement membrane, of eosinophilic infiltration of the mucous membrane, and of the musculature of the bronchioles and bronchi.

The pathology of acute anaphylaxis in the guinea pig is chiefly characterized by bronchial stenosis and emphysema. Efforts have been made to explain the bronchial stenosis on the basis either of a spastic contraction of the smooth bronchial musculature, or on that of an edema of the bronchial lumen. Some support the theory of initial bronchial edema. Recently Warren and Dixon[84] showed that the bronchial obstruction of anaphylactic shock does not result solely from contraction of bronchial smooth muscle. Bronchial constriction occurs in the early stages of shock and is rapidly succeeded by edema. According to Schultz and Jordan[68] it is more probable in true anaphylaxis of the guinea pig that the muscular constriction is situated in the bronchioles, where there is an absence of cartilage and a relative increase in the size of the muscles.

The bronchial mucosa does not lie smoothly on the inner wall of the bronchi in the guinea pig but forms longitudinal folds which are seen, on cross section, as

villiform projections. The loose submucous cell tissues under certain circumstances allow these folds to be removed from the substratum. They are drawn together until they touch and produce a valvular-like obstruction.

It is probably fair to assume that in all inhalant respiratory exposures edema plays the dominant role because of the direct contact of the antigen with the lining of the bronchial structures.

Roentgen Studies on Guinea Pigs.—Kallos and Pagel found that before and during the dyspneic attacks roentgen observation of the lungs filled with iodized poppyseed oil showed that in an attack there was occlusion of the middle bronchi and acute high grade emphysema. The bronchial occlusion was conditioned by the bronchial spasm, by swelling of the bronchial mucous membrane, and by plugs of secretion.

Studies by Barclay et al show that the preponderant effect occurs in the bronchial mucosa when heavy opaque materials are used to demonstrate changes in the respiratory tree. These artificial media, of course, are not entirely comparable to antigens inhaled for the purpose of inducing experimental asthma.

Roentgen Studies on Human Beings.—Steinberg[73] correlated roentgen and postmortem observations. He commented as follows: "It may be assumed that an attack is ushered in by bronchospasm, but all the evidence is against bronchoconstriction being responsible for the entire trend of events preceding and following the peak of an attack." He expressed the opinion that an asthmatic paroxysm is essentially due to bronchial occlusion by mucus as a result of hypersecretory activity of the bronchial mucous glands.

Rigler and Koucky[66] made a roentgen study of the bronchi of asthmatic patients by means of iodized oil. In the early stages the caliber of the bronchi was distinctly narrowed. Later some of the bronchi failed to show shadows of iodized oil, which indicated that occlusion had taken place. The authors concluded that the first effect is due to spasm of the bronchial muscle. Mucus accumulates within the lumens of the bronchi. A plug is formed, partially obstructing the bronchus. Air may be inspired past the occlusion but is expelled less rapidly. Emphysema is thus produced. During the asthmatic attack the spastic bronchial muscle clamps down around this plug, aggravating the occlusion.

Involvement of the Exudative and Bronchomuscular System.—The observations of Huber and Koessler and of Kallos and Pagel make it plain that in human beings as well as in guinea pigs the allergic reaction of the tissues is not confined to the smooth muscle fiber system alone. It involves the whole organic system which serves exudative processes of endothelium, epithelium, capillaries, and glands. The rational attitude toward the question, it appears, is to realize that the exudative and the bronchomuscular systems act simultaneously in the production of stenosis. In some cases one is more concerned than the other, but both are always involved to some extent.

As demonstrated in the preceding pages, shock reactions observed in the animal after the inhalation of specific antigens are as a rule sublethal, resembling the shock reactions in the asthmatic patient. Occasional deaths do occur in guinea pigs shocked through the inhalant route. In such animals the lung is typical of injectant anaphylaxis, which results from the direct absorption of the antigen into the circulation. In sublethal inhalant allergy the antigen comes into direct local contact with the sensitized tissues of the bronchi, bronchioles, and alveoli. The regional sensitization demonstrated in our experiments with dry antigens seems to corroborate such a hypothesis.

It becomes apparent then that death in a human subject resulting from an injection of serum may be likened to anaphylactic death in the guinea pig sensitized and

shocked by parenteral injection. The pathologic changes in bronchial asthma in the human subject must be compared with the secondary changes observed in guinea pigs which were subjected to repeated dust inhalation.

In conclusion, then, we might state that the pathologic processes causing anaphylactic death cannot be compared with those of bronchial asthma. When the pathologic changes of asthma in the human being are compared with those observed in the guinea pig subjected to repeated direct inhalation of specific antigens, we are actually comparing similar phases of the allergic phenomenon: namely, chronic allergic respiratory states in both instances. The changes then are fundamentally indistinguishable in the two species.

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(Continued on Page 702)

In Memoriam

CECIL WALKER DINGMAN

We regret to announce the death of Dr. Cecil Walker Dingman, Associate Fellow of the College. At his death he was a member of the Medical Department of United Air Lines, Mills Field, Municipal Airport, South San Francisco, California.

Doctor Dingman was born June 2, 1900, was graduated from the Lincoln, Nebraska, High School in 1918, and received his degree of B.Sc. in 1923 and M.D. in 1925 from the University of Nebraska. He served his internship in the U. S. Army, Fitzsimons General Hospital, Denver, Colorado. He took up postgraduate studies at the Army Medical School, Army Field Service School, Flight Surgeons School, and the Advanced EENT School. He also took postgraduate training in allergy under the direc- of Dr. Leon Unger at the Cook County Hospital, Chicago, in 1948. He served in the United States Army from the time of his graduation until 1942, and was with United Air Lines from that time until his death. He practiced medicine for twenty-six years and was licensed to practice in Nebraska, Illinois, Colorado, California, and Oregon. He was a member of the American Medical Association and the Aero Medical Association. Doctor Dingman remained single. He had many friends and was well liked by his associates. We deeply regret his departure.

SOME PSYCHOLOGICAL ASPECTS OF THE TREATMENT OF PATIENTS WHO HAVE FOOD ALLERGIES

(Continued from Page 664)

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540 Brooklawn Avenue

Letter to the Editor

To the Editor:

In view of the recent publicity given to the possible relationship between special types of paralytic poliomyelitis and vaccination against whooping cough, diphtheria, tetanus or, indeed, the injections of any biological or medicinal substances, including penicillin and procaine, the statement of the National Foundation for Infantile Paralysis on this subject should be summarized at this time. The Foundation points out that certain studies indicate that when injections are given in a limb within the month immediately preceding an attack of paralytic poliomyelitis, the limb injected seems to be paralyzed more frequently than the corresponding limbs of cases where there was no history of injections during that month. Where there had been injections given more than a month before the onset of poliomyelitis, the relationship was not found. The statement goes on to clarify the situation further:

"The studies do *not* show that injections for the prevention of whooping cough, diphtheria, tetanus, or injections of other medicinal substances, are the cause of poliomyelitis. The great majority of cases of poliomyelitis give no history of recent injections. There is no evidence that poliomyelitis infection is any more frequent among persons who receive such injections than among those who do not. The possibility that an injection may in some way tend to convert an otherwise non-paralytic into a paralytic infection should be considered although it lacks proof. If established, it would mean that an injection of any of the substances mentioned, at a time when poliomyelitis is abnormally prevalent in the community, may entail some small added risk to the person receiving it. There is no reason to believe that the added risk would extend beyond the month immediately following the injection, or that any added risk exists at all if injections are given at a time when poliomyelitis is not prevalent in the community.

"In addition to the studies on human beings, there have been two reports of experiments on animals. These suggest that the interval between an injection of the virus of poliomyelitis and onset of paralysis is shorter in those animals previously injected with certain immunizing substances.

"However, these animal experiments do not give any real basis for deciding on the safety of immunizing a child in a given situation. Physicians are well aware that many medical procedures involve calculated risk. The relative risks of giving or withholding an injection must be weighed in each individual case. Whether an injection of a medicinal substance is needed can be determined only by the physician dealing with a specific patient. He must determine in each case when injections are and are not warranted.

"Studies on the relationship of paralytic poliomyelitis to injections of medicinal substances have not been completed, nor have the results been properly evaluated as yet. Results reported to date are tentative and should not be considered at this time as final evidence. They should be considered only in the light of a warning against indiscriminate injections during periods of poliomyelitis epidemics.

It is of the utmost importance that these hypotheses and theories be considered as tentative. A concerted effort must be made to establish the relationships between vaccination and residual paralysis in the vaccinated limb on a more statistical basis than the publicity has warranted. It is anticipated that both The American College of Allergists and The American Academy of Allergy will shortly co-operate to ascertain what the facts are.

Harold A. Abramson, M.D.

133 East 58th Street
New York, N. Y.

News Items

COLLEGE INSTRUCTIONAL COURSE AND CONVENTION

The College Annual Graduate Instructional Course will be conducted April 4, 5 and 6 preceding the Eighth Annual Session, April 7, 8, and 9, both at the Hotel William Penn, Pittsburgh. Chairman of the Instructional Course is Dr. Hal Davison with Dr. James A. Mansmann acting as Co-Chairman. The over-all program committee consists of Dr. Giles A. Koelsche, Chairman; Dr. Harold A. Abramson, President, ACA; and Dr. Fred W. Wittich, Secretary-Treasurer, ACA. Dr. J. Warrick Thomas, President-Elect, is Chairman of the General Session.

Below are listed the five sections into which Convention papers will be divided, together with the name and address of each chairman:

Section on Otolaryngologic Allergy
Dr. Walter E. Owen, Chairman
1242 Jefferson Building
Peoria 2, Illinois

Section on Pediatric Allergy
Dr. Bret Ratner, Chairman
50 East 78th Street
New York 21, New York

Section on Industrial Allergy
Dr. Mayer A. Green Chairman
6111 Jenkins Arcade
Pittsburgh 22, Pennsylvania

Section on Psychosomatic Allergy
Dr. John H. Mitchell, Chairman
695 Bryden Road
Columbus, Ohio

Section on Dermatologic Allergy
Dr. Adolph Rostenberg, Jr., Chairman
Allergy Unit, University of Illinois
College of Medicine
1853 West Polk Street
Chicago 12, Illinois

Registration for the Convention will commence Sunday, April 6, at 2:00 p.m. At 4:00 p.m. there will be tea at the University of Pittsburgh, with a conducted tour of the Nationality Rooms of the Cathedral of Learning. The Entertainment Committee of Pittsburgh, whose names were published in the May-June issue of the ANNALS, are arranging entertainment for the ladies and guests attending, consisting of a tour of the H. J. Heinz plant, a buffet snack, a technicolor film, and many other features.

Monday will be devoted to the General Session, consisting of papers on hay fever, asthma, drugs, rheumatism, and arthritis. On the morning of Tuesday, April 8, the presidential address will be given by Dr. H. A. Abramson, followed by the guest speaker, Dr. Alexander Wiener, whose topic is "The Solution of Certain Fundamental Immunologic Problems by Studies on Rh Sensitization." After the business meeting two simultaneous round table luncheons will be held: one on psychosomatic allergy, with Dr. Abramson as moderator; and one on pediatric allergy, with Dr. Jerome Glaser as moderator. At 2:00 the section on psychosomatic allergy will begin, presided over by Dr. John H. Mitchell, followed by the section on pediatrics, with Dr. Bret Ratner as chairman. The evening will be devoted to a cocktail party and a banquet with excellent music and a floor show.

On Wednesday morning Dr. Adolph Rostenberg, Jr., will preside over the dermatologic section and Dr. Walter E. Owen over the otolaryngologic section. At 12:30

there will be a round table luncheon on dermatologic allergy, Dr. A. B. Loveman, moderator, and at the same time another round table luncheon on otolaryngologic allergy, Dr. George Shambaugh, Jr., moderator. At 2:00 Dr. Mayer Green will preside at the section on industrial allergy.

The Graduate Instructional Course promises to be the most complete of its kind ever given. Although clinical allergy in all its phases will be stressed, the basic principles are presented adequately by authorities in their particular field. Much new material will be covered at this instructional course. It will cover diagnosis and treatment, not only of the common allergic diseases but all of the more recent symptom complexes which are now recognized as being on an allergic basis. There will also be demonstrations on diagnostic procedures, both office and laboratory. The features on Friday evening will be two round tables: one on psychodynamics and one on the diagnosis and treatment of asthma. Saturday the morning will be devoted to an authoritative presentation on the diagnosis and treatment of allergic dermatosis. There will be a luncheon at 12:45, followed by a luncheon lecture on the integration of allergy and internal medicine. An innovation is the symposium on industrial allergy, comprising lectures on allergy and industry, occupational dermatoses, allergic reactions produced by industrial dust, and respiratory tract allergies—effects from chemical air pollution. Following this will be a demonstration of office and laboratory procedures in allergy. Saturday evening two round tables will be held: one on industrial allergy and one on allergic skin diseases. Sunday's lectures will cover allergy to air-borne fungi, the botany of hay fever pollens, eye and ear allergy, rhinitis and sinusitis, immunization with virus vaccine, and the use of histamine, ACTH, and cortisone in the treatment of allergic diseases. The course will be concluded by miscellaneous lectures on food allergy, allergy in children, and headaches.

Large and comprehensive technical and scientific exhibits will add greatly to the educational value of this allergy assembly and will merit frequent visits to the exhibition hall. There will be intermissions twice each day in the scientific program as well as luncheon and dinner intermissions which will allow profitable visits to the exhibits.

About the first of the year all members will receive hotel reservation cards. Please fill these out promptly and mail to the hotel. All members will receive a mimeographed copy of the final program, and this will also appear in a subsequent issue of the ANNALS. Elaborate printed programs will be available only for those who attend the convention.

The officers are anticipating the largest attendance in the history of the College.

INTERNATIONAL ASSOCIATION OF ALLERGISTS

With the appearance of this issue of the ANNALS, the First Congress of the International Association of Allergists held at Zurich, Switzerland, September 23-29, will have completed its meeting. The Congress was followed by a Symposium on the Influence of Pituitary Gland and Adrenal Cortex on Biological Reactions, arranged by the Swiss Academy of Medical Sciences, October 1 and 2.

Those representing the American Academy of Allergy were Dr. Francis M. Rackemann, Regent; Dr. Samuel Feinberg, Committee on Constitution and By Laws; Dr. Howard Osgood, Committee on Nomenclature; and Dr. Horace Baldwin. For the American College of Allergists, in the absence of Dr. Harold A. Abramson, President, the Board of Regents elected Dr. Ethan Allan Brown to represent the President; Dr. Fred W. Wittich as a delegate on the Committee on Constitution and By Laws; and Dr. Hal Davison on the Committee on Nomenclature.

Practically all the known existing national allergy societies were represented of-

ficially and some other societies unofficially. Representatives attended from the following countries: Argentina, Australia, Belgium, Bolivia, Brazil, Canada, Chile, Colombia, Cuba, Denmark, England, Finland, France, Germany, Holland, Hungary, Israel, Italy, Mexico, Norway, Paraguay, Peru, Philippine Islands, Poland, Puerto Rico, Scotland, South Africa, Spain, Sweden, Switzerland, United States, Uruguay, and Wales.

The honorary president of the IAA is Dr. Ph. Etter, Swiss Federal Councillor. The executive committee of the First Congress is: President, Prof. Dr. Ch. W. Loeffler; General Secretary, Prof. Dr. A. S. Grumbach; Treasurer, Director A. G. Mann. Chairman of the Executive Committee of the IAA is Dr. Fred W. Wittich.

POSTGRADUATE COURSE IN PEDIATRIC ALLERGY

A postgraduate course in pediatric allergy is announced, under the direction of Bret Ratner, M.D., F.A.C.A., Professor of Clinical Pediatrics and Associate Professor of Immunology, and members of those departments, at New York Medical College, Flower and Fifth Avenue Hospital. Thirty sessions will be held from November 7, 1951, through May 28, 1952, on Wednesdays, 9:00 a.m. to 4:00 p.m. The fee is $300.

This course consists of lecture-seminars, laboratory, clinical procedures, clinic work, ward rounds, and animal experimentation. Lecture-seminars cover the basic principles as well as the diagnosis and treatment of allergy in children and applied immunology.

Applicants must be certified in pediatrics or have the requirements for certification. The group will be limited. Application should be made to the Dean, New York Medical College, 106th Street and Fifth Avenue, New York 29, N. Y.

RESEARCH FELLOWSHIP IN PEDIATRIC ALLERGY

Two fellowships are offered under the direction of Bret Ratner, M.D., F.A.C.A., in the departments of Pediatrics and Immunology, New York Medical College, 106th Street and Fifth Avenue, New York 29, N. Y.

These fellowships in pediatric allergy are full time. One starts July 1, 1951, the other January 1, 1952. Applicants must be certified in pediatrics or have the requirements for certification. The fellowships run from one to two years and will consist of intensive training in immunology and animal research pertaining to the field of hypersensitiveness; and intensive study of allergic children, which will include skin testing, laboratory work, and clinical follow-up, as well as clinical research. Applicants who have had previous training in chemistry and/or immunology and who are desirous of a career in research will be given preference.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Annual Postgraduate Course in Diseases of the Chest, sponsored by the Council on Postgraduate Medical Education and the New York State Chapter of the American College of Chest Physicians, will be presented at the Hotel New Yorker, New York City, November 12-17, 1951.

This course will emphasize the recent advancements in the diagnosis and treatment of chest diseases. The course is open to all physicians, but the number of registrants will be limited. Tuition fee is $50.00; applications will be accepted in the order in which they are received. Applications should be sent to the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

The Interim Session of the American College of Chest Physicians will be held at the Ambassador Hotel, Los Angeles, California, on December 2 and 3, 1951. Dr.

Edward W. Hayes, Monrovia, California, is chairman of the general arrangements committee; Dr. Alfred Goldman, Beverly Hills, of the scientific program committee.

The Board of Regents of the American College of Chest Physicians offers a cash prize award of $250.00 to be given annually for the best original contribution, preferably by a young investigator, on any phase relating to chest disease. For complete details, write to Henry C. Sweany, M.D., Chairman, Committee on College Essay, at the Chicago address listed above.

PENNSYLVANIA ALLERGY ASSOCIATION

The fall meeting of the Pennsylvania Allergy Association will be held on Wednesday, October 3, 1951, at Geisinger Hospital, Danville, Pa. The program committee consists of Drs. F. W. Davison (chairman), Lester Fowle, and Robert Dickey.

Following a meeting of the board of regents, the papers listed below will be read: Pediatric Allergy by E. F. Rabe, M.D.; Practical Aspects of Allergy in Otolaryngology by D. H. Walker, M.D.; Preliminary Report on Researches in Nummular Eczema by Lester Fowle, M.D.; An Allergic Tour Through the Gastrointestinal Tract by James Mansmann, M.D.; Allergy in Tuberculosis by John Packard, M.D.; and Psychosomatic Aspects of Allergy by Peter Kwiterovich, M.D.

The day will be concluded by cocktails, dinner, and entertainment.

CALIFORNIA SOCIETY OF ALLERGY

At the third annual meeting of the California Society of Allergy, the following officers were elected for a term of one year:

President: Samuel H. Hurwitz, M.D., F.A.C.A., 490 Post Street, San Francisco, Calif.

President-Elect: M. Coleman Harris, M.D., F.A.C.A., 414 North Camden Drive, Beverly Hills, Calif.

Secretary-Treasurer: Grace Talbott, M.D., F.A.C.A., 909 Hyde Street, San Francisco, Calif.

WILLIAM H. DAVIS

Friends will grieve to learn of the recent death of William H. Davis, vice president in charge of distribution for Burroughs Wellcome & Co., Tuckahoe, New York.

CAFERGOT SUPPOSITORIES IN MIGRAINE

(Continued from Page 620)

6. Horton, B. T.; Ryan, R., and Reynolds, J. L.: Clinical observations on use of EC 110, new agent for treatment of headache. Proc. Staff Meet., Mayo Clin., 23:105 (Mar. 3) 1950.
7. Kadish, A. H.: Clinical observations on the rectal and oral use of various ergot derivatives in headache. New England J. Med., 242:581 (Apr. 13) 1950.
8. Kadish, A. H.: Clinical observations on use of EC 110 in various types of headaches. Gen. Pract. Clin., 6:151 (Apr.) 1949.
9. Moench, L. G.: Clinical use of EC 110, new headache remedy (preliminary report). Dis. Nerv. System, 10:143 (May) 1949.
10. O'Sullivan, Mary E.: Termination of one thousand attacks of migraine with ergotamine tartrate. J.A.M.A., 107:1208 (Oct. 10) 1936.
11. Ryan, R. E.: Cafergone for relief of headache. Postgrad. Med., 5:330 (Apr.) 1949.
12. Wolff, H. G.: Headache and other head pain. Oxford Medical Publications, 1948.

1601 Argonne Place, N.W.

BOOK REVIEWS

1950 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. By Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 497 pages, 67 figures. Price $5.00. Chicago: The Year Book Publishers, 1951.

The latest edition of the Year Book of Dermatology and Syphilology as usual is replete with the up-to-the-minute progress of the subject. With the introduction of ACTH and cortisone in dermatology for the past two years, they have become the major factor of progress in this field. Many skin diseases are benefited by the use of these hormones, which, however, are limited in curative effect. Remissions depend upon continued use of these steroids, with consequent limitation of value. Since there are many variable side reactions from the use of these hormones, their administration must be meticulously controlled. Aside from their therapeutic benefits, they afford implements for the study of diseases and reactions of the skin. The authors are of the opinion that ACTH and cortisone promise more for dermatologists and their patients than the vitamins, the sulfonamides, and the antibiotics combined.

The Year Book does not, however, confine itself to ACTH and cortisone. Much has been done to clarify the indications for the topical and/or systemic use of aureomycin, chloramphenicol, and terramycin in infectious dermatoses and in "minor" venereal diseases, as well as the results of their preliminary clinical evaluation in syphilitic infections. Work on the relation of the treponemal antibody to the nonsyphilitic positive reactions in serologic tests for syphilis has been extended. Encouraging progress in venereology is indicated by studies made on the life cycle of the spirochete by means of the phase microscope and improved staining methods. Recent knowledge on the nature of the lupus erythematosus phenomenon is also advanced.

Practical therapy is applied throughout the text. The diseases of hypersensitivity are given their proper recognition.

The illustrations are good.

PROCEEDINGS OF THE THIRD INTERNATIONAL CONGRESS OF THE INTERNATIONAL SOCIETY OF HEMATOLOGY. Carl V. Moore, M.D., Editor; 220 contributors. 593 pages, numerous figures. Price: cloth bound $10.00, paper bound $8.00. New York: Grune & Stratton, 1951.

This book contains the entire proceedings of the Third International Congress of the International Society of Hematology held at Cambridge, England, August 21-25, 1950. The Editorial Committee was composed of such authorities as L. Berman, J. Bernard, S. Haberman, J. Hill, H. Ludin, R. MacFarland, S. Mettier, R. Race, and E. Storti.

The contributions appear as complete manuscripts, as abstracts, or as titles of presentations made before the Congress. These represent essentially the latest developments in the field of hematology, possible only at an international congress. As with all international societies, the purpose of this society is for furnishing the means for a free exchange of scientific information by all workers from any country interested in the broad field of hematology. Its membership therefore includes clinicians, pathologists, clinical pathologists, biochemists, physiologists, immunologists, geneticists, microbiologists, and anatomists. This volume represents the tremendous investigative activity which is focused on the blood, the blood-forming organs, and the diseases associated with them.

There are five sections, the first containing fifty-four chapters on the anemias and related subjects. Occasionally a chapter is published in German or French. Section Two contains twenty-five chapters on immunohematology. There are forty-nine chapters on leukemia and related diseases, and thirty-nine chapters on coagulation, purpura, and related subjects. There are indices and an appendix. The book is actually a tome on the subject. The photographs are good and the paper stock excellent. The general practitioner and the specialist as well as the medical student should study these proceedings.

PEDIATRIC ALLERGY. By Robert Chobot, M.D. 284 pages, 14 tables. Price $4.50. New York: McGraw-Hill Book Company, 1951.

Any book on pediatric allergy by an outstanding authority is most welcome to the student, the pediatrician, and the general practitioner. Actually, allergy as now defined invites controversy. A book which aims to clarify divergent opinions based on authoritative clinical and investigative experience is always of value.

The pendulum of the importance of focal infection in contributing to the causes of allergic symptoms seems to have reached a normal rhythm. Accumulating evidence that focal infection plays an important role as the cause of allergic symptoms cannot be depreciated. The text is free from redundancy, is simple, succinct, and practical. Substantial evidence of the author's concepts is supplemented with a number of actual illustrative case histories from the author's files.

SURGICAL MANAGEMENT OF NASAL ALLERGY

(Continued from Page 587)

and often leave the patient more of an invalid than he was previously.

The same applies to the management of chronic sinusitis and to the treatment of asthma by surgical procedures on the sinuses. This method of treatment seldom affords more than temporary relief from the asthma. In a large series of such patients who had been subjected to the external ethmo-fronto-sphenoidectomy, relief varied from six weeks to two years duration. All, however, eventually had a return of the asthma and in most with more pronounced symptoms.

The improvement in our management of nasal and sinus conditions is due largely to our better understanding of nasal physiology and our appreciation of the importance of the rôle played by allergy in rhino-sinusitis.

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